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ABSTRACTS

Abstracts presented at the 18th International Taurine Meeting

Marrakesh, Morocco

April 7–13, 2012

Welcome to the 18th International Taurine Meeting!

The organizing committee wishes to welcome you to Marrakech. Sir Winston Churchill was particularly taken by Marrakech… "Here, surrounded by its extensive palm-groves that have sprung out of the desert, the traveler may rest assured that he will never tire of the majestic view of the snow-covered Atlas Mountains…" We are sure that you will be equally taken by both Marrakech and Morocco.

This year, the conference is highlighting the "Mystique of Taurine." This marks the first time that our conference is to be held in Africa. As a result, we present here data from investigators from five of the six continents (sadly taurine research has yet to hit Antarctica). We present here information on the roles of taurine in a variety of organ systems, from the brain to the reproductive system and every system in between. As you are keenly aware, there is certainly a mystique to taurine. Is it beneficial or harmful? Does it protect cells or induce cell death? Can it be used in conjunction with another molecule to benefit health or cause death? The answer (or at least a hint to the answer) to these and other questions lies within this body of works.

Because of the success of this meeting, the organizing committee wishes to gratefully acknowledge the following:
Taisho Pharmaceutical Co., Ltd., Tokyo Japan
Professor Dr. Gert Lubec, FRSC (UK), Medical University of Vienna and Editor in Chief of AMINO ACIDS
Dr. Claudia Panuschka, Springer Wien, Senior Editor Biomedicine/Life Sciences
Dr. Portia Formento, Springer US, Editor Biomedicine

On behalf of the organizing committee, I welcome you to the 18th international Taurine Meeting and I wish you a very pleasant stay in Marrakesh

Best wishes,

Abdeslem El Idrissi, Ph.D
Chair, Organizing Committee
18th International Taurine Meeting
Marrakesh, Morocco
April 7–13th
http://www.taurine2012.org

18th International Taurine Meeting

Marrakesh, Morocco

April 7–13, 2012

Saturday, April 7

7:00 pm Cocktail Reception Hour/Welcome Party
8:45 pm Group Dinner

Sunday, April 8

Platform Presentations

9:00 am Opening remarks Dr. Abdeslem El Idrissi

9:10–10:10 am

Lecture I Chairperson: Dr. Stephen Schaffer

TAURINE AND HEARTY TOPICS
Junichi Azuma; Clinical Pharmacology and Pharmogenomics; Department of Pharmacy; Hyogo University of Health and Science, Kobe, Japan

10:10–10:30 am Coffee Break

10:30–12:30 pm
Session I—Function of Taurine in the Cardiovascular system

Chairperson: Dr. Sanya Roysommuti

10:30 **The role of taurine deficiency under stress in cardiac and skeletal muscles: a study in taurine transporter gene knockout mice**
[1]Takashi Ito, [2]Stephen W. Schaffer [1]Junichi Azuma
[1]Hyogo University of Health Sciences, School of Pharmacy, Kobe, Japan
[2]University of South Alabama, College of Medicine, Mobile, AL 36688, USA

11:00 **Perinatal taurine supplementation affects neural control of arterial pressure via estrogen receptors in adult female rats**
Atcharaporn Thaeomor[1,2], J. Michael Wyss[3], Stephen W. Schaffer[4], Dusit Jirakulsomchok[1], and Sanya Roysommuti[1]
[1]Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand, [2]School of Biology, Institute of Science, Suranaree University of Technology, Nakhonratchasima 30000, Thailand, [3]Department of Cell Biology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, USA, and [4]Department of Pharmacology, College of Medicine, University of South Alabama, Mobile, AL 36688, USA

11:30 **11:30 Mechanism underlying calcium-dependent contractile defect in taurine transporter knockout heart**
Chian Ju Jong[1], KC Ramila[1], Takashi Ito[2], Junichi Azuma[2], Stephen Schaffer[1]
[1]University of South Alabama, Department of Pharmacology, College of Medicine, Mobile, AL 36688, [2]Hyogo University of Health Sciences, School of Pharmacy, Kobe, Japan

12:00 **Gender specific effects of taurine on cardiovascular function**
Evelyn Okeke, Francoise Sidime, Lorenz Neuwirth, Xin Yan, Abdeslem El Idrissi
Department of Biology, City University of New York, College of Staten Island, USA

12:30–2:00 Lunch

2:15 Excursion "**La visite de ville"** A guided tour of the city of Marrakesh and its monuments

7:30 Dinner at the Hotel

Monday, April 9

9:00–10:00

Lecture II Chairperson: Dr. Russell W. Chesney

There is a taurine-linked disease known as melas
[1]Stephen Schaffer, [1]Chian Ju Jong and [2]Junichi Azuma
[1]University of South Alabama, School of Medicine, Department Pharmacology, Mobile, AL USA, [2]Hyogo University of Health Sciences, Department Pharmacy, Kobe, Japan

10:00–10:20 am Coffee Break

Lecture III Chairperson: Dr. Chaekyun Kim

10:20–11:20
Part-1: Taurine and the Immune system—state of art and new roles of taurine in innate immunity.
Part-2: "Are taurine haloamines (TauCl/TauBr) good candidates for the treatment of biofilm-associated infections"
Janusz Marcinkiewicz[1], Magdalena Strus[2], Maria Walczewska[1], Anna Gacoń[4]
[1]Department of Immunology and [2]Department of Microbiology, Jagiellonian University Medical College, Cracow, Poland

11:20–12:35
Session II—Taurine and the Immune System
Chairperson: Dr. Janusz Marcinkiewicz

11:20 **Protection of cells from oxidative stress-induced cytotoxicity and resolution of inflammation by taurine chloramine**
Chaekyun Kim
Laboratory of Leukocyte Signaling Research, Department of Pharmacology and BK21 Program, Inha University School of Medicine, Incheon 400-712, Korea

11:50 **Effect of taurine chloramine on differentiation of human preadipocytes into adipocytes, and expression of adipokines in differentiated adipocytes**
Kyoung Soo Kim, Hyun-Mi Choi, Hye-In Ji, Chaekyun Kim, Ha won Kim
East-West Bone and Joint Disease Research Institute, Kyung Hee University Hospital at KANGDONG, 149 Sangil-dong, Gangdong-gu, Seoul, 134-727, Korea, Laboratory for Leukocyte Signaling Research, Department of Pharmacology and BK21 Program, Inha University School of Medicine, Incheon 400-712, Republic of Korea, Department of Life Science, University of Seoul, Seoulsiripdaero 163, Dongdaemun-gu, Seoul 130-743, Korea

12:20 **Perspective on taurine research**
Ekkehart Trenkner
New York State Institute for Basic Research and Developmental Disability and Center of Developmental Neuroscience and Developmental Disability, Staten Island, NY 10314, USA

12:35–2:00 Lunch

2:00–6:00 pm
Poster Session

3:45–4:15 Coffee Break

Monoaminergic activity is increased following electroconvulsive therapy (ECT), but less is known about amino acids.
Martin Samuelsson
Division of Psychiatry, Department of Clinical and Experimental Medicine, Faculty of Health Sciences Linköping, Sweden

Synthesis of carbohydrate–taurine derivatives
Ji Yun Kim, Hye Jeong Cho and Sung Hoon Kim
Department of Chemistry, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul 143-701, Korea

The effect of bisphosphonates drug and hyperglycemic condition on taurine transport at inner blood–retinal barrier
Young-Sook Kang
Sookmyung Women's Univ. College of Pharmacy, Chungpa-dong, Yongsan-gu, Seoul Korea (South)

Taurine tissue concentrations in metabolic disease measured by a cheap enzyme based assay.
Katrine Seide Pedersen, Niels Grunnet, Bjørn Quistoff, Ole Hartvig Mortensen
Department of Biomedical Sciences, University of Copenhagen, Denmark

The effect of taurine on glucose and lipid homeostasis in fructose-fed Wistar rats
Lea H. Larsen[1], Laura K.H. Orstrup[1], Svend H. Hansen[2], Niels Grunnet[1], Bjørn Quistorff[1] and Ole H. Mortensen[1]
[1]Department of Biomedical Sciences, Cellular and Metabolic Research Section, University of Copenhagen, Copenhagen, Denmark, [2]Department of Clinical Biochemistry, Rigshospitalet and Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Comparative evaluation of the efffects of hypotaurine, taurine and thiotaurine on alterations of the cellular redox status and activities of antioxidant and glutathione-related enzymes by acetaminophen in the rat
M. Acharya and C.A. Lau-Cam
Department of Pharmaceutical Sciences; St. John's University; College of Pharmacy and Allied Health Professions; Jamaica, NY 11439, USA

Effects of dietary taurine supplementation on serum taurine and adipokine level in diet-induced obesity rat model
*Jeong Soon You1, Xu Zhao1, Sung Hoon Kim2, Kyung Ja Chang1**
[1]Department of Food and Nutrition, Inha University, Incheon, Korea, [2]Department of Chemistry, Konkuk University, Seoul, Korea

Effects of taurine on iNOS-dependent DNA damage in heavy exercise skeletal muscle by inhibiting NF-κB signaling pathway
Hiromichi Sugiura[1, 2], Shinya Okita[1], Toshihiro Kato[1], Toru Naka[1], Shosuke Kawanishi[1], Yoshiharu Oshida[2], Ning Ma[1]
[1]Faculty of Health Science and Pharmaceutical Sciences, Suzuka University of Medical Science, Suzuka, Mie 510-0293, Japan, [2]Department of Sports Medicine, Graduate School of Medicine, Nagoya University, Nagoya 464-8601, Japan

Taurine and adipokines level in 8 week body weight control program in obese female college students
*Jeong Soon You1, Ji Yeon Park1, Xu Zhao1, Jin Seok Jeong2, Mi Ja Choi3, Kyung Ja Chang1**
Department of Food and Nutrition, Inha University, Incheon, Korea

Evaluation of taurine as anti-alopecia agent using *C. elegans*
Hyemin Kim and Dong-Hee Lee
University of Seoul, Seoul, Korea

Taurine inhibited LPS induced declines in neurogenesis in DG
Gaofeng wu[1], Takashi Matsuwaki[2], Yoshinori Tanaka[2], Jiancheng Yang[1], Keitaro Yamanouchi[2], Jianmin Hu[1] and Masugi Nishihara[2*]*
[1]Department of Animal Science and Veterinary Medicine, Shenyang Agricultural University, Shenyang, 110866, China, [2]Department of Veterinary Physiology, Veterinary Medical Science, The University of Tokyo, Tokyo 113-8657, Japan

Characterization of anti-stress effect of taurine on plant cells cultured in vitro
Hyemin Kim and Dong-Hee Lee
University of Seoul, Seoul, Korea

The effects of chronic taurine supplementation on motor learning
A. Santora, A. El Idrissi, L. Newirth, and W. J. L'Amoreaux
The College of Staten Island of The City University of New York, Center for Developmental Neuroscience and Developmental Disabilities (CDNDD), New York, USA

Taurine enhances anticancer activity of cisplatin in human cancer cells
An Keun Kim, Taehee Kim
College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea

Effects of taurine on male sexuality in rats
*Jiancheng Yang, Gaofeng Wu, Qiufeng Lv, Shumei Lin and Jianmin Hu**
College of Animal Science and Veterinary Medicine, Shenyang Agricultural University, Shenyang, 110866, People's Republic of China

Protective effect of taurine on tri-ortho-cresyl phosphate (TOCP) induced cytotoxicity in C6 glioma cell
Yachen Li, Fengyuan Piao
Department of Occupational and Environmental Health, Dalian Medical University, Dalian, Liaoning 116044, China

Evaluation of taurine levels in plasma and aqueous humour from normal domestic dogs: a pilot study
REOVVA members[1], Nathalie Neveux[2,3], José-Alain Sahel[3], Serge Picaud[4] and Nicolas Froger[4]
[1]Réseau Européen d'Ophtalmologie Vétérinaire et de Vision Animale; [2] Unité de recherche EA 4466, stress cellulaire: Physiopathologie, stratégies nutritionnelles et thérapeutiques innovantes. Faculté de Pharmacie. Université Descartes Paris France, [3]Service Inter-hospitalier de biochimie, CHU Cochin-St-Vincent de Paul, AP-HP, Paris. France.; [4]Institut de la Vision, INSERM UMR_S 968, UPMC Univ Paris 06, CNRS UMR 7210 17, rue Moreau 75012 Paris, France

Effect of dietary taurine and arginine supplementation on bone mineral density in growing female rats
*Mi-Ja Choi *. Kyung-Ja Jang***
*Department of Food and Nutrition, Keimyung University, Daegu, Korea, **Department of Food and Nutrition, Inha University, Incheon, Korea

Effect of taurine feeding on bone mineral density and bone markers in the rat
Choi, Mi-Ja, Seo, Ji-na*
Department of Food and Nutrition, Keimyung University, Daegu, Korea

The role of taurine on the skeletal muscle cell differentiation
Teruo Miyazaki, Akira Honda, Tadashi Ikegami, Yasushi Matsuzaki
Tokyo Medical University Ibaraki Medical Center, Japan

Taurine chloramine increases HO-1 expression and activity by promoting Nrf2 activation via oxidative modification of Keap1
In Soon Kang[1], Shuyu Piao[1,2,3], Young-Nam Cha[2], and Chaekyun Kim[1,2,3,]*
[1]Laboratory of Leukocyte Signaling Research, [2]Department of Pharmacology, and [3]BK21 Program, Inha University School of Medicine, Incheon 400-712, Korea

Taurine has no effect on inhibition of human adipocyte differentiation and change of adipokine expression in adipocyte induced by endoplasmic reticulum stress
Kyoung Soo Kim, Hye-In Ji, Hyung-In Yang, Myung Chul Yoo
Kyung Hee University Hospital at Gangdong, Seoul, Korea

Free radical scavenging activities of taurine by electron spin resonance spectrometry
Sun Hee Cheong[1], Sung Hoon Kim[2] and Kyung Ja Chang[3]
[1]Department of Applied Biological Chemistry, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan, [2]Department of Chemistry, Konkuk University, Seoul 143-701, Korea, [3]Department of Food and Nutrition, Inha University, Incheon 402-751, Korea

Taurine promotes glucose uptake in cultured rat skeletal L6 myotubes
*Sun Hee Cheong and Kyung Ja Chang**
Department of Applied Biological Chemistry, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan, *Department of Food and Nutrition, Inha University, Incheon 402-751, Korea

Effects of taurine supplementation upon food intake and central insulin signaling in malnourished mice fed a high fat diet (HFD)
Camargo RL[1], Batista TM[1], Ribeiro RA[2], Velloso LA[3], Boschero AC[1], Carneiro EM[1]
[1]Departamento de Biologia Funcional e Estrutural, Universidade Estadual de Campinas, [2]Núcleo em Ecologia e Desenvolvimento Sócio-Ambiental, NUPEM, Universidade Federal do Rio de Janeiro, [3]Departamento de Clínica Médicas, Faculdade de Ciências Médicas, Universidade Estadual de Campinas

Taurine (TAU) supplementation restores insulin secretion and reduces ER Stress markers in protein-malnourished mice
Batista TM[1], da Silva PMR[1], Amaral AG[2], Ribeiro RA[1,3], Boschero AC[1], Carneiro EM[1]
[1]Departamento de Biologia Funcional e Estrutural, Universidade Estadual de Campinas, [2]Divisão de Nefrologia e Medicina Molecular, Universidade de São Paulo, [3] Núcleo em Ecologia e Desenvolvimento Sócio-Ambiental, NUPEM, Universidade Federal do Rio de Janeiro

Behavioral and biochemical studies of antidepressant-like effects of taurine
Atsushi Toyod; Wataru Lio
College of Agriculture, Ibaraki University; 3-21-1 Chuo Ami Ibaraki 300-0393 Japan

Additional effects of taurine on the benefits of BCAA intake for the delayed-onset-muscle-soreness and muscle-damage induced by high-intense eccentric exercise
Song-Gyu Ra[1], Teruo Miyazaki [2], Keisuke Ishikura[3], Hisashi Nagayama[4], Takafumi Suzuki[1], Seiji Maeda[1], Masaharu Ito[5], Yasushi Matsuzaki[6], Hajime Ohmori[1]
[1]Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, [2]Center for Collaborative Research, Tokyo Medical University Ibaraki Medical Center, Ami, Japan, [3]Sports Research and Development Core, University of Tsukuba, Tsukuba, Japan, [4]School of Health and Physical Education, University of Tsukuba, Tsukuba, Japan, [5]Livence Co. Inc., Chuo, Tokyo, Japan, [6]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Tokyo Medical University Ibaraki Medical Center, Ami, Japan

Thiotaurine prevents apoptosis of human neutrophils: a putative role in inflammation
Elisabetta Capuozzo, Laura Pecci, Alessia Baseggio Conrado, Silvestro Duprè, Mario Fontana
Dipartimento di Scienze Biochimiche, Sapienza Università di Roma, Piazzale Aldo Moro, 5, 00185, Rome, Italy

Correlations between dietary taurine intake, dietary habit score and fatigue in Korea college students
So Yoon Park, Jeong Soon You, Kyung Ja Chang
Department of Food and Nutrition, Inha University, Incheon 402-751, Korea

Dietary nutrients intake including taurine, dietary habit score and dietary quality according to the alcohol consumption level in Korean male college students
Jeong Soon You, So Young Kim, Kyung Ja Chang
Department of Food and Nutrition, Inha University, Incheon 402-751, Korea

Protection by taurine and thiotaurine against biochemical and cellular alterations induced by diabetes in a rat model
R. Budhram and C.A. Lau-Cam
Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY, USA

The effects of taurine and thiotaurine on oxidative stress in the aorta and heart of diabetic rats
E. Mathew, M. Barletta and C.A. Lau-Cam
Department of Pharmaceutical Sciences; St. John's University; College of Pharmacy and Allied Health Professions; Jamaica, NY 11439, USA

Rising taurine and ethanol concentrations in nucleus accumbens interact to produce the positive reinforcing effects of alcohol
Mia Ericson, PeiPei Chau, Rhona B. Clarke, Louise Adermark & Bo Söderpalm
Addiction biology unit, department of Psychiatry and Neurochemistry, Gothenburg, Sweden

Taurine provides neuroprotection for retinal ganglion cells in different cellular and animal models of glaucoma
Nicolas Froger, Lucia Cadetti, Henri Lorach, Julie Dégardin, Dorothée Pain, Élisabeth Dubus, Valérie Forster, Manuel Simonutti, José-Alain Sahel and Serge Picaud
Institut de la Vision, UMRS 968, 17, rue Moreau 75012 Paris, France

6:00–6:50 **"Kaftan night"** ladies will be dressed with a Moroccan Kaftan for dinner. There will be a large selection of Kaftans to choose from.

7:00 **Depart the hotel for "La soirée Marocaine au restaurant EL BAHIA"**

Tuesday, April 10

Lecture IV Chairperson: Dr. Susan L Greenwood

9:00–10:00

Comparative evaluation of taurine and thiotaurine as protectants against experimental diabetes-induced nephropathy in a rat model
K. Pandya, R. Budhram and C.A. Lau-Cam
Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York, USA

10:00–10:30 am Coffee Break

10:30–12:30 pm

Session III—Taurine and Diabetes

Chairperson: Dr. William L'Amoreaux

10:30 **Taurine ameliorates hyperglycemia and dyslipidemia by reducing insulin resistance and leptin level in Otsuka Long-Evans Tokushima fatty (OLETF) rats with long duration of diabetes**

Kyoung Soo Kim[1], Da Hee Oh[2], Jung Yeon Kim[4], Bong Gn Lee[3], Jeong Soon You[5], Kyung Ja Chang[5], In-Kyung Jeong[2]
[1]East-West Bone and Joint Research Institute, Kyung Hee University Hospital at Gangdong, Kyung Hee University, 149 Sangil-dong, Gangdong-gu, Seoul, Republic of Korea, [2]Department of endocrinology, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, 149 Sangil-dong, Gangdong-gu, Seoul, Republic of Korea, [3]Core Research Laboratory, Clinical Research Institute, Kyung Hee University Hospital at Gangdong, Kyung Hee University, 149 Sangil-dong, Gangdong-gu, Seoul, Republic of Korea, [4]Department of Pathology, Inje University Sanggye Paik Hospital, 761-1 Sanggye 7-dong, Nowon-gu, Seoul, Republic of Korea, [5]Department of Food and Nutrition, Inha University, 100 Inha-ro, Nam-gu, Incheon, Republic of Korea

11:00 **Preventive roles of taurine in alloxan-induced diabetes**

Francoise Sidime, Xin Yan, Lorenz Neuwirth, William L'Amoreaux, Abdeslem El Idrissi
College of Staten Island and Graduate Center, City University of New York, NY 10314, USA

11:30 **Renin-angiotensin system and estrogen attenuates glucose–insulin dysregulation in adult female rats that are perinatally depleted of taurine**

Sanya Roysommuti[1], Atcharaporn Thaeomor[1], Dusit Jirakulsomchok[1], and J. Michael Wyss[2]
[1]Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand and [2]Department of Cell Biology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, USA

12:00 **Taurine affects release of insulin and GABA in Hit-T15 β cell line via calcium flux**

Christina M. Cuttitta, Sara R. Guariglia, and William J. L'Amoreaux
Department of Biology, City University of New York, College of Staten Island, USA

12:30–2:00 **Lunch**

2:15 Excursion **"La visite des Souk"** A guided tour of the souks and outdoor markets displaying some of the finest Moroccan crafts and threadworks available

7:30 **Dinner at the Hotel**

Wednesday, April 11

9:00–10:00 am

Lecture V Chairperson: Dr. Eitan Friedman

Neuropsychopharmacological actions of taurine

Shailesh P. Banerjee, Andre Ragnauth, Mervan S. Agovic, Iman Jashanmal, Louis Vidal, Eitan Friedman
Department of Physiology, Pharmacology and Neuroscience, Sophie Davis School of Biomedical Education at CCNY, City University of New York, NY 10031, USA, Neuroscience Subprogram, Doctoral Programs in Biology and Psychology, Graduate Center of the City University of the City University of New York, NY 10016, USA

10:00–10:30 am Coffee Break

Session IV—Taurine and its actions on the nervous system

Chairperson: Dr. Shailesh P. Banerjee

10:30 **Direct interaction of taurine with the NMDA glutamate receptor sub-type via multiple mechanisms**

Christopher Y. Chan, Herless S. Sun, Sanket M. Shah, Mervan S. Agovic, Ivana Ho, Eitan Friedman, Shailesh P. Banerjee
Department of Physiology, Pharmacology and Neuroscience, Sophie Davis School of Biomedical Education at CCNY, City University of New York, NY 10031, USA and Neuroscience Subprogram, Doctoral Programs in Biology, Graduate Center of the City University of New York, NY 10016, USA

11:00 **Metabotropic effect of taurine regulation of potassium channels via 5-HT2A serotonin receptors**

Wen Shen
Department of Biomedical Science, Charles E Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL 33431, USA

11:30 **Perinatal taurine exposure affects patterns of autonomic nerve activity in adult male rats**
Sawita Khimsuksri[1, 2], J. Michael Wyss[3], Jarin Paphangkorakit[2], Dusit Jirakulsomchok[1], and Sanya Roysommuti[1]
[1]Department of Physiology, Faculty of Medicine and [2]Department of Oral Biology, Faculty of Dentistry, Khon Kaen University, Khon Kaen 40002, Thailand; [3]Department of Cell Biology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

12:00 **Effects of acute vs. chronic taurine treatment on context fear aversive conditioning in mice**
Lorenz S. Neuwirth[1,2], Nicholas Volpe[2] & Abdeslem El Idrissi[1,2]
[1]The CUNY Graduate Center and [2]The College of Staten Island (CUNY), Staten Island, NY, USA

12:30–2:00 Lunch

2:00–2:45

Lecture VI Chairperson: Dr. Howard Prentice

Neuro-protective mechanism of taurine—role of endoplasmic reticulum
Jang-Yen Wu, Howard Prentice and Chunliu Pan
Florida Atlantic University, Charles E. Schmidt College of Medicine, Boca Raton, FL 33431, USA

2:45–6:15 pm

Session V—Taurine and neuronal effects

Chairperson: Dr. Simo Oja

2:45– **Taurine exerts robust protection against hypoxia and glucose deprivation in human neuroblastoma cell culture**
Howard Prentice[1], Chunliu Pan[2] and Jang-Yen Wu[1]
[1]Department of Biomedical Science, Florida Atlantic University, Boca Raton, FL 33431, USA, [2]Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL 33431, USA

3:15– **Changes in gene expression at inhibitory synapses in response to taurine treatment.**
Chang Hui Shen Eugene Lempert, Isma Butt and Abdeslem El Idrissi
Biology and Biochemistry Department; College of Staten Island/CUNY, Staten Island, NY 10314, USA

3:45–4:15 Coffee break

4:15– **Lethality of taurine and alcohol co-administration in 7 day-old, adult and old mice**
Andrey Taranukhin[1,2], Kalervo Kiianmaa[3], Pirjo Saransaari[1] and Simo S. Oja[4]
[1]University of Tampere, Medical School, Tampere, Finland, [2]Sechenov Institute of Evolutionary Physiology and Biochemistry, Laboratory of Comparative Somnology and Neuroendocrinology, St.-Petersburg, Russia, [3]National Institute for Health and Welfare, Department of Alcohol, Drugs and Addiction, Helsinki, Finland, and [4]Tampere University Hospital, Department of Paediatrics, Tampere, Finland

4:45– **The mechanism of taurine protection against endoplasmic reticulum stress in stroke related conditions in primary neuronal cell culture**
Jang-Yen Wu[1] Chunliu Pan[2], and Howard Prentice[1]
[1]Department of Biomedical Science and [2]Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL 33431, USA

5:15–6:15

Lecture VII Chairperson: Dr. Wen Shen

Regulation of taurine release by neurotransmitter receptors
Simo S. Oja and Pirjo Saransaari
Tampere University Hospital, Department of Paediatrics and University of Tampere, Medical School, Finland

7:00 Depart the hotel for "La soirée CHEZ ALI"

Thursday, April 12

Lecture VIII Chairperson: Dr. Xiaobin Han

9:00–10:00

Differential regulation of taut by vitamin D3 and retinoic acid via VDR/RXR in LLC-PK1 and MCF-7 cells
Russell W. Chesney and Xiaobin Han
Department of Pediatrics, University of Tennessee Health Science Center, and the Children's Foundation Research Center at Le Bonheur Children's Hospital, Memphis, TN, USA

10:00–10:30 am Coffee Break

10:30–11:30

Session VI—Taurine and Taurine Transporter

Chairperson: Dr. Takashi Ito

10:30– **Reduced placental taurine transporter (TauT) activity in pregnancies complicated by maternal obesity and pre-eclampsia**
Michelle Desforges, Andrea Ditchfield, Chloe.R.Hirst, Colin.P.Sibley, J.D.Glazier and Susan.L.Greenwood
Maternal and Fetal Health Research Centre, The University of Manchester, Manchester M13 9WL, UK

11:00 **Knockdown of TauT expression impairs human embryonic kidney 293 cell development**
Xiaobin Han and Russell W. Chesney
Department of Pediatrics, University of Tennessee Health Science Center, and the Children's Foundation Research Institute at Le Bonheur Children's Hospital, Memphis, TN, USA

11:30–

Session VII—Taurine in Nutrition and metabolism

Chairperson: Dr. Ole Hartvig Mortensen

11:30– **Gestational taurine availability and fetal programming of metabolism in C57BL/6 mice**
Orstrup LKH, Larsen LH, Pedersen KS, Grunnet N, Quistorff B, Mortensen OH
Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Denmark

12:00 **Taurine and mitochondrial bioenergetics**
Svend H. Hansen
Department of Clinical Biochemistry, Rigshospitalet and Faculty of Health Sciences, University of Copenhagen, Denmark

12:30–2:00 Lunch

2:00– **Taurine and fish nutrition: where do we stand on the use of this mythical molecule?**
Cláudia Aragão, Wilson Pinto, Maria Teresa Dinis and Luís E.C. Conceição
CCMAR, Universidade do Algarve, Campus de Gambelas. Faro, Portugal

2:30– **The physiological role of taurine during fish development—relevant aspects for the aquaculture industry**
Wilson Pinto, Ivar Rønnestad, Maria Teresa Dinis and Cláudia Aragão
CCMAR, Universidade do Algarve, Campus de Gambelas. Faro, Portugal

3:00– **The ability of taurine as a marker for the identification of natural Calculus Bovis and its substitutes**
Kayoko Shimada[1], Yuko Azuma[1], Masaya Kawase[3], Toshiharu Takahashi[4], Stephen W. Schaffer[5] and Kyoko Takahashi[1,2]
[1]Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan, [2]The Museum of Osaka University, Osaka, Japan, [3]Nagahama Institute of Bio-Science and Technology, Shiga, Japan, [4]Kyoto University Research Reactor Institute, Kyoto University, Osaka, Japan, [5]School of Medicine, University of South Alabama, Mobile, AL, USA

3:30– **Effect of arsenic on the expressions of thyroid hormone receptor genes in mice brains and protection of taurine**
Fengyuan Piao, Yachen Li
Department of Occupational and Environmental Health, Dalian Medical University, Dalian, Liaoning 116044, People's Republic of China

4:00 Coffee break

4:30–7:30

Session VIII—Interdisciplinary session

Chairperson: Dr. Abdeslem El Idrissi

The effect of folic acid on gamma-aminobutyric acid type A (GABAA) receptor beta1 (gabrb1) possible implication in autism
Kizzy Vasquez[1], Mohamed Junaid[2], Abdeslem El Idrissi[1,3]
[1]Biology Department, College of Staten Island, New York, NY 10314, USA, [2]New York Institute for Basic Research in Developmental Disabilities, Staten Island NY, USA, [3]CUNY Graduate Center, NY, USA

Rat GABAergic neural developmental assessment of anxiety, fear potentiation, learning, memory, and pilocarpine induced temporal lobe epilepsy in the rat following chronic low level lead exposure
Lorenz S. Neuwirth and Abdeslem El Idrissi
The CUNY Graduate Center and The College of Staten Island (CUNY), Staten Island, NY, USA

IGF-1 Role in VEGF-dependent vascular formation of human retinal microvascular endothelial cells
Janto Tachjadi, Jonathan F. Blaize, William J. L'Amoreaux
The College of Staten Island (City University of New York); The Graduate Center, CUNY; Advanced Imaging Facility, College of Staten Island, CUNY, USA

The influence of hepatocyte growth factor during outer segment phagocytosis by retinal pigment epithelium
Jonathan F. Blaize[1,2,3], Janto Tachjadi[1,2,3], Christopher Marra[1,3], Seth Brawer[1,3], William J. L'Amoreaux[1,2,3]
[1]The College of Staten Island (City University of New York); [2]The Graduate Center, CUNY; [3]Advanced Imaging Facility, College of Staten Island, CUNY, USA

Effect of *Nigella sativa* oil on GABAA-receptor mediated neurobehaviors in mice
Simon Ng,[1]Lorenz S Neuwirth,[3,4] and Abdeslem El Idrissi[2,3,4],
College of Staten Island; [2]Department of Biology, College of Staten Island; [3]Doctoral Program in Biology, Neuroscience, The Graduate Center, The City University of New York, 365 Fifth Avenue, New York, NY 10016, USA

Neurobehavioral effects of prenatal exposure to dibutyl phthalate in juvenile mice
Francoise Sidime [1, 2], Chuhyon Corwin [1], A. Marsillo[1, 2], A. El Idrissi [1, 2]
[1]Neuroscience Department, College of Staten Island, 2800 Victory Blvd, Staten Island, New York, 10314, USA, [2]Graduate Center, 365 5th Ave, New York, NY, 10016, USA

Alteration of the photic entrainment of the circadian system in a mouse model of diabetic retinopathy
Lahouaoui H. [1, 2], Cooper H.M.[2], Dkhissi-Benyahya O. [2] and, Bennis M.[1]
[1]Lab of Pharmacology, Neurobiology and Behavior (URAC-37), Faculty of Sciences Semlalia, Marrakech, Morocco, [2]INSERM U-846, Stem Cell and Brain Research Institute, Department of Chronobiology, Bron, France; [2]UCBL, Lyon1, France

Dopamine modulation of latent inhibition in animal model of Schizophrenia
Ouhaz Z., Ba M'hamed S., Bennis M.
Lab of Pharmacology, Neurobiology and Behavior (URAC-37), Cadi Ayyad University, Marrakech, Morocco

Effects of exposure to fenugreek seeds aqueous extract during gestation on locomotor development in mice
L. Khalki[1], JC viemari[2], H. Bras[2], L Vinay[2], Z. Sokar[1], S. Ba M'hamed
[1]Lab of Pharmacology, Neurobiology and Behavior, Associated Unit to CNRST (URAC-37), Cadi Ayyad University, Marrakech, Morocco; [2]Institut de Neurosciences de la Timone, P3M team, UMR 7289-CNRS-AMU, Marseille, France

Effects of Nicotine and alkaloids of tobacco plant on extracellular level of dopamine in the striatum and the nucleus accumbens: behavioral correlation
Khalki Hanane[1], Navailles Sylvia[2], Camille Piron[2], Chait Abderrahman[1], De Deurwaerdère Philippe[2].
[1]Laboratory of Pharmacology, Neurobiology and Behavior (URAC-37), University Cadi Ayyad, Faculty of Sciences Semlalia, Marrakesh, Morocco, [2]Institut des Maladies Neurodégénératives, CNRS UMR 5293, Bordeaux, Université Bordeaux 2, Bordeaux, France

Effects of prenatal stress by forced swimming on the neurobehavioral development in mice pups

Aimran, N. Zouhairi, L. Khalki, M. Bennis and S. Ba M'hamed
Laboratory of Pharmacology, Neurobiology and Behavior (URAC-37), University Cadi Ayyad, Faculty of Sciences Semlalia, Marrakesh, Morocco

Functional recovery after a lesion of the medullar corticospinal tract in barrelless mice

H. Nait Taleb Ali[1], S. Scotto-Lomassese[2], I.Dusart[3], P. Gaspar[2] and M.Bennis[1]
[1]Laboratoire de Pharmacologie, Neurobiologie et Comportement (URAC-37), Université Cadi Ayyad, FSSM, Marrakech, Morocco, [2]INSERM U839, Institut du Fer-à-Moulin, Paris, France, [3]UPMC Univ. Paris 06, UMR 7102, NPA, Paris, France

Thinner exposure affects spatial memory in C57 mice

M. Ben El Fakir, M. Bennis, S. Ba M'hamed
Laboratory of Pharmacology, Neurobiology and Behavior (URAC-37), Cadi Ayyad University Faculty of Sciences Semlalia, Marrakesh, Morocco

The characterization of Pb^{2+} toxicity in the rat cardiovascular system: an assessment of Pb^{2+} induced pathophysiology

Evelyn Okeke, Lorenz Neuwirth, Abdeslem El Idrissi
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Role of voltage sensitive calcium channels (VSCCs) in the maturation of the GABAergic system in the fragile X syndrome

Xin Yan and Abdeslem El Idrissi
Biology Department, College of Staten Island City University of New York, NY, 10314, USA, and Neuroscience Subprogram, Doctoral Programs in Biology Graduate Center of the City University of the City University of New York, NY, 10016, USA

Prenatal stress in rats influences the vaginocervical sensitivity: study of c-fos expression in the spinal cord of the offspring

Nadia Zouhairi, Sâadia Ba M'hamed, Mohamed Bennis
Laboratory of Pharmacology, Neurobiology and Behaviour (URAC-37), Cadi Ayyad University, Marrakech, Marrakech, Morocco

Lectures

Taurine regulation of cardiac function and peripheral hemodymanics

Abdeslem El Idrissi

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GABA plays an important role in the modulation of cardiovascular function by acting not only within the brain but also within peripheral tissues. We found that IV injection of GABA to male rats caused hypotension and tachycardia. Taurine produced similar effects to those caused by GABA. Blockade of $GABA_A$ receptors with picrotoxin antagonized all effects of GABA and taurine. Picrotoxin itself caused significant increases in mean arterial pressure and bradycardia. We further confirm the vasoactive properties of taurine and GABA using isolated aortic rings preparations. Mechanical responses of circular aortic rings to pharmacological agents were measured by an isometric force transducer and amplifier. We found that bath application of GABA and taurine to the aortic rings caused vasodilation which was blocked by picrotoxin. Interestingly, picrotoxin alone induced a constriction of the aortic ring in the absence of exogenously added GABA, suggesting a tonic activation of $GABA_A$ receptors. Furthermore, inhibition of glutamic acid decarboxylase (GAD), the rat-limiting enzyme of GABA synthesis, by isoniazide or mercaptoproprionic acid induced a vasoconstriction of the aortic rings. The effect of these inhibitors was abolished by bath application of GABA. These data suggest that isolated aortic rings synthesize and release GABA which activates $GABA_A$ receptors and induces vasodilation. The presence of GAD and $GABA_A$ receptors in smooth muscle cells of the aorta and large vessels was confirmed by immunofluorescence. Additionally, we found that the endothelial cells express high levels of taurine transporters and have previously shown that taurine activate $GABA_A$ receptors. Thus, we hypothesize that GABA and taurine either blood-borne or released from smooth muscle cells of arteries activate $GABA_A$ receptors and causes vasodilation. This would partially antagonize the effects of epinephrine and provides a novel mechanism for the regulation of blood flow and arterial resistance.

The role of taurine deficiency under stress in cardiac and skeletal muscles: a study in taurine transporter gene knockout mice

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Taurine deficiency associates with some pathological alterations and aging-impaired tissue function. However, the roles of taurine deficiency in the tissue dysfunction have not been fully clarified.

To elucidate the role of taurine depletion in tissues, we generated the mice lacking taurine transporter gene (TauTKO). Lacking of TauT gene resulted in taurine depletion in heart and skeletal muscle as well as other tissues. In heart, functional deterioration and fibrosis were observed in old TauTKO mice, but not in young mice. Induction of heart failure markers, such as atrial natriuretic peptide, brain natriuretic peptide and beta-myosin heavy chain, was enhanced in older TauTKO mice than younger mice. These results indicate that lack of TauT in mice leads to an aging-related cardiomyopathy. On the other hand, forced exercise test showed TauTKO mice exhibited the reduction in exercise endurance performance. In skeletal muscle, structural abnormalities, such as atrophy and myofibril breakdown, were detected in muscle of TauTKO. Moreover, deteriorations of metabolic response during exercise, including accumulation of lactate, were observed in TauTKO mice. Therefore, exercise endurance of TauTKO mice is likely due to the structural and metabolic disorder. These data suggest that taurine deficiency increased the susceptibility against physiological stress in heart and skeletal muscles.

Perinatal taurine supplementation affects neural control of arterial pressure via estrogen receptors in adult female rats

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Perinatal taurine depletion and high sugar diets alter neural and renal control of arterial pressure via the renin-angiotensin system in adult rats. This study tests the hypothesis that perinatal taurine supplementation predisposes adult female rats to the adverse arterial pressure effects of high sugar intake via the renin-angiotensin system rather than estrogen. Female Sprague–Dawley (SD) rats were fed normal rat chow with 3% taurine (TS) or water alone (C) from conception to weaning. Their female offspring were fed normal rat chow with either 5% glucose in tap water (TSG, CG) or tap water alone (TSW, CW). At 7–8 weeks of age, the female offspring's renin-angiotensin system or estrogen receptors were inhibited by captopril (CW + Cap, CG + Cap, TSW + Cap, TSG + Cap) or tamoxifen (CW + Tam, CG + Tam, TSW + Tam, TSG + Tam), respectively. Body weight, heart weight, kidney weight, mean arterial pressures (MAP), and heart rates were not significantly different among control groups (without captopril or tamoxifen). Captopril (but not tamoxifen) decreased MAP but not heart rates in all groups. In TSG compared to TSW, CW and CG groups, baroreflex sensitivity of heart rate (BS-HR) and renal nerve activity (BS-RN) were significantly decreased. The BS-HR in TSG was not altered by either captopril or tamoxifen, and tamoxifen (but not captopril) restored TSG BS-RN to CW or CG control levels but not captopril treatment. Perinatal taurine imbalance (either increase or decrease) did not disturb sympathetic and parasympathetic nerve activity in the adult rats on high or basal sugar intake. Tamoxifen increased the sympathetic but decreased the parasympathetic activity less in TSG and TSW groups vs. CW and CG groups. Inhibition of the renin-angiotensin system did not affect the autonomic nerve activity in any group. The present data indicate that in adult female rats receiving high sugar intake, chronic perinatal taurine supplementation alters autonomic nervous system control of arterial pressure via estrogen receptors and not via the renin-angiotensin system.

Mechanism underlying calcium-dependent contractile defect in taurine transporter knockout heart

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Cardiomyopathy is a common pathological consequence of taurine depletion. While the exact mechanism underlying taurine depletion-mediated cardiomyopathy remains unclear, it is known that taurine depletion causes a shift in calcium sensitivity in myofibrils, resulting in impaired contractility. Indeed, we showed that hearts from taurine transporter knockout mice demonstrated a decline in the Ca^{2+} sensitivity of contractile proteins, as exemplified by the Ca^{2+} dependence of myofribrillar ATPase. A potential trigger for cardiac contractile defects is oxidative stress, a major complication of taurine deficiency, as evidenced by reduced aconitase activity and decreased glutathione redox ratio. We hypothesized that oxidative stress alters Ca^{2+} sensitivity of the taurine-depleted heart through a mechanism involving protein kinase C (PKC) activation. PKC phosphorylates troponin I, which acts as the calcium sensor in cardiac myofilaments. In support of this theory, we found that taurine deficiency alters both the distribution and levels of specific PKC isoforms. PKC-ε is translocated from the cytosol to the membrane, while the expression of PKC-δ is elevated in both the cytosolic and membrane fractions of taurine deficient hearts. Although the specific PKC isoforms involved in the underlying mechanism remain to be elucidated, clearly, taurine depletion activates PKC, leading to troponin I phosphorylation. Phosphorylation of troponin I, as observed in taurine-depleted heart, reduces the binding affinity of calcium to troponin C, thereby decreasing contractile function and calcium sensitivity of the myofibrils. Therefore, our study shows that taurine depletion impairs cardiac contractility via PKC-mediated phosphorylation of troponin I.

Gender specific effects of taurine on cardiovascular function

Evelyn Okeke, Francoise Sidime, Lorenz Neuwirth, Xin Yan, Abdeslem El Idrissi

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Taurine is a sulfur containing amino acid that functions as an inhibitory neurotransmitter. It also acts as an allosteric transmitter, mimicking gamma-aminobutyric acid (GABA) by binding to the GABAA receptor not only in the brain but also in the peripheral tissue. Therefore, taurine plays an important role in the modulation of cardiovascular functions. Our study was designed to elucidate the differences between acute and chronic taurine supplementation, and investigate its possible biochemical changes effecting the blood pressure. In our experiment, we designed two treatment groups, the acute treatment that received the taurine (43 mg/kg) via i.p. injection, and the chronic treatment that received the taurine (0.05%) in the drinking water. We have shown previously that taurine activates the $GABA_A$ receptor by measuring the chloride uptake in cerebellar granule cells, therefore we suggest that taurine causes vasodilation, hence a decrease in blood pressure. While in the acute treatment the blood pressure was significantly lowered in both genders 15 min post injection, the blood pressure of the chronic treated female rats was interestingly significantly higher and male rats were not affected. In addition to a seemingly gender specific effect on blood pressure in this treatment group, both genders showed a significant increase in heart rate. Thus, we suggest that an acute treatment of taurine may aid in lowering blood pressure, while the chronic treatment seem to be counter effective, as our data shows.

There is a taurine-linked disease known as MELAS

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Mitochondrial diseases are a heterogenous group of disorders that arise from mutations in either mitochondrial or nuclear genomes and produce deficiencies in the mitochondrial respiratory chain. One of these disorders, MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) is commonly associated with a point mutation in $tRNA^{Leu(UUR)}$, which diminishes the posttranslational modification of the wobble position uridine residue. The modification resulting in the conversion of uridine to 5-taurinomethyluridine enhances the interaction of UUG codons with their anticodon, facilitating the decoding of the UUG codon. A reduction in 5-taurinomethyluridine formation diminishes the expression of several complex I subunits, with ND6 showing the largest decline. In MELAS the reduction in 5-taurinomethyluridine content is related to a mutation, although reductions in 5-taurinomethyluridine are presumably also caused by significant declines in the mitochondrial taurine pool. Thus, the taurine transporter knockout mouse model (TTKO) mimics the wobble defect of MELAS, as supported by several observations. First, complex I activity is significantly reduced in MELAS and the TTKO mouse. Second, the levels of several mitochondria encoded proteins, all of which become subunits of complex I, are reduced in TTKO mice. Third, taurine deficiency leads to a reduction in respiration and a shift in favor of anaerobic metabolism, a phenomenon consistent with all mitochondrial diseases. Fourth, both MELAS and taurine deficiency exhibit lactic acidosis and are associated with the development of myopathies and CNS defects. Fifth, oxidative stress is a concern in MELAS and is one of the likely causes of the cardiomyopathy in TTKO mice. Although taurine plays a central role in MELAS, it is important to emphasize that taurine is a major regulator of energy metabolism in both normal and diseased cells.

Are taurine haloamines (TauCl and TauBr) good candidates for the treatment of biofilm-associated infections?

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Biofilms are consortia of micro-organisms (sessile cells) that form on various surfaces including mucosal membranes or teeth. Bacterial biofilms cause many human infections such as chronic sinusitis, acne vulgaris or periodontal diseases. These infections are persistent as they show increased resistance to antibiotics and host defence system (e.g. phagocytosis).

Taurine chloramine (TauCl) and taurine bromamine (TauBr) are the products of activated neutrophils, resulting from the reaction between taurine with hypochlorous acid (HOCl) and hypobromous acid (HOBr), respectively. It has been shown in vitro that TauCl and

TauBr exert anti-microbial properties against planktonic form pathogenic bacteria. Moreover, clinical studies have shown that both haloamines are effective in the local treatment of skin and mucose infections, including biofilm-related infections (acne vulgaris, otitis media). The above data suggest that TauCl and TauBr are good candidates for the therapy of chronic bacterial infections, especially in patients who have already developed antibiotic resistance.

Our preliminary studies conducted to prove this hypothesis suggest:

- taurine haloamines more effectively kill planktonic form of bacteria than sessile bacteria cells, hidden in biofilm
- TauBr at non-cytotoxic concentrations is able to inhibit in vitro the development of *P.aruginosa* biofilm but cannot destroy the preformed biofilm
- DNAse and *N*-acetylcysteine, well known biofilm inhibitors do not interfere with bactericidal activity of taurine haloamines

Therefore, we conclude that taurine haloamines, especially TauBr, are promising candidates for local combined therapy of biofilm-related infections, aplicated together with other anti-biofilm agents.

Protection of cells from oxidative stress-induced cytotoxicity and resolution of inflammation by taurine chloramine

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Taurine chloramine (TauCl) is produced by the activated neutrophils in a reaction between taurine and HOCl by myeloperoxidase system, and protects cells from the cytotoxicity of HOCl. TauCl provides cytoprotection against inflammatory injury by inhibiting the overproduction of inflammatory mediators, such as TNF-alpha, IL-6, IL-8, prostaglandins, NO and O_2^-. In our study, TauCl increased the expression of Nrf2-regulated antioxidant proteins like HO-1, Prx-1 and Trx-1 in macrophages. TauCl increased the cytosolic content of Nrf2 and its nuclear translocation as well as its binding to ARE. However, TauCl did not alter the DNA binding of other transcription factors like NFκB, AP-1 and CREB. The knock down of Nrf2 expression by its siRNA reduced the TauCl-induced HO-1 expression. TauCl increased the oxidized form of Keap1 and decreased the content of biotin-PEAC5-maleimide-bound Keap1. In summary, TauCl produced abundantly by activated neutrophils promotes the oxidative modification of Keap1 and thus enhances nuclear translocation of Nrf2 that results in the elevation of HO-1 expression and HO activity required for efficient removal of free heme in cells undergoing oxidative stress. Similarly, the elevated expression of other antioxidant enzymes by TauCl may protect normal cells from cytotoxic oxidative stress that occurs at inflammatory lesion.

Effect of taurine chloramine on differentiation of human preadipocytes into adipocytes, and expression of adipokines in differentiated adipocytes

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We investigated whether taurine chloramine (TauCl), which is endogenously produced by immune cells such as macrophages that infiltrate adipose tissue, affects the differentiation of preadipocytes into adipocytes or modulates the expression of adipokines in adipocytes. To study the physiological effects of TauCl on human adipocyte differentiation and adipokine expression, preadipocytes were cultured under differentiation conditions for 14 days in the presence or absence of TauCl. Differentiated adipocytes were also treated with TauCl in the presence or absence of IL-1β (1 ng/ml) for 7 days. The culture supernatants were analyzed for adipokines such as adiponectin, leptin, IL-6, and IL-8. At concentrations of 400–600 μM, TauCl significantly inhibited the differentiation of human preadipocytes into adipocytes in a dose-dependent manner. It did not induce the dedifferentiation of adipocytes or inhibit fat accumulation in adipocytes. Expression of major transcription factors of adipogenesis and adipocyte marker genes was decreased after treatment with TauCl, in agreement with its inhibition of differentiation. At a concentration of 600 μM, TauCl slightly modulated the production of adipokines in adipocytes. However, TauCl significantly blocked the decreased production of adiponectin and leptin caused by IL-1β stimulation. It also inhibited the increased production of IL-6 and IL-8 caused by IL-1β stimulation in a dose-dependant manner. These results suggest that TauCl may inhibit the differentiation of preadipocytes into adipocytes and modulate the expression of adipokines in adipocytes. Thus, TauCl or more stable derivatives of TauCl could potentially be a safe drug therapy for obesity-related diseases.

Perspective on taurine research

Ekkehart Trenkner

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Increasing numbers of scientists, including myself, have dedicated their research careers to understanding the properties and mechanisms of action of taurine. This "wonder" molecule seems to be involved in so many cellular and physiological actions that it is by any measure remarkable. Taurine is one of the few known naturally occurring free sulfonic acids and it is derived out of cysteine, a sulfur-containing amino acid. Taurine was first isolated from ox bile in 1827 by German scientists Friedrich Tiedemann and Leopold Gmelin and was named after the Latin word Taurus, which means bull or ox.

The diverse actions of taurine in almost all tissues examined, may indicate that taurine is regulating a cellular process that is as ubiquitous as taurine actions. Some of the mechanisms of taurine actions are not receptor-dependent. We have previously suggested that taurine mediates some of its actions through intracellular calcium regulation. The abundance of cellular events mediated by taurine are consistent with the broad role of calcium at the cellular level. We have reported that taurine plays an important role in regulating both intracellular and intra-mitochondrial calcium homeostasis. The functional significance of this is neuroprotection against excitotoxicity, oxidative stress and increased energy production. The long term effects of this neuroprotective action can be observed on cognitive function in mice, supplemented with taurine over long periods of time.

Comparative evaluation of taurine and thiotaurine as protectants against experimental diabetes-induced nephropathy in a rat model

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Nephropathy is a long-term complication of diabetes mellitus and the most common cause of end-stage renal failure. Poor glycemic control and hypertension are recognized as major determinants of the metabolic, functional, morphological and structural renal changes associated with this clinical problem. In addition, there is considerable evidence to suggest that persistent hyperglycemia can lead to the intracellular generation of free radicals capable of inducing altered renal cell function and injury. Taking into account the proven effectiveness of antioxidants in preventing experimentally induced diabetes in laboratory animals, the present study was carried out with the specific purpose of comparing the effectiveness of two known antioxidants, the β-aminosulfonate taurine (TAU) and the β-aminothiosulfonate thiotaurine (TTAU), in preventing biochemical, functional and histological alterations indicative of diabetic nephropathy. In the study, streptozotocin (60 mg/kg, intraperitoneally) was used to induce type 2 diabetes mellitus in Sprague–Dawley rats. Starting on day 15 and continuing up to day 56, the rats received a daily single 2.4 mmol/kg oral dose of a sulfur-containing compound (TAU or TTAU) or a 4 U/kg subcutaneous dose of isophane insulin (INS). Rats receiving only oral physiological saline as a treatment served as controls. After obtaining a 24 h urine sample, the animals were sacrificed by decapitation on day 57, and their blood and kidneys immediately collected. Diabetic rats exhibited marked hyperglycemia, hypoinsulinemia, hypoproteinemia, hyponatremia, hyperkalemia, azotemia, hypercreatinemia, increased plasma TGF β_1, increased urine output and fractional Na^+ excretion, decreased urine Na^+ and K^+, decreased urine/plasma cretinine ratio, proteinuria and hypocreatinuria. Without exceptions, all the treatment compounds were found to markedly and variously attenuate these changes. Further evidence on protection by the treatment compounds on diabetic nephropathy was provided by the results of histological examination of stained kidney sections showing decreased morphological changes, the absence of edema and of inflammatory cells, and a normal basement membrane relative to sections from untreated diabetic animals. In most instances, protection by INS and TTAU was about equal and of a greater magnitude than that by TAU.

Taurine ameliorates hyperglycemia and dyslipidemia by reducing insulin resistance and leptin level in Otsuka Long-Evans Tokushima fatty (OLETF) rats with long duration of diabetes

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Aims/hypothesis: To determine whether taurine supplementation improve metabolic disturbances and diabetic complications in type 2 diabetic animal model.
Methods: We investigated whether taurine has therapeutic effects on glucose and lipid metabolism and diabetic complications in Otsuka Long-Evans Tokushima fatty (OLETF) rats, an animal model of type 2 diabetes. Fifty week-old OLETF rats with chronic diabetes were fed a diet supplemented with taurine (2%) for 12 weeks. During the experimental period, we checked serum glucose levels and glycated hemoglobin levels (HbA1c) and did oral glucose tolerance tests (OGTTs). After taurine supplementation, urine microalbumin and heart, aorta, and kidney tissues were investigated for diabetic complications. Serum was analyzed for levels of adiponectin, leptin, insulin and lipid.
Results: Taurine lowered blood glucose levels over 12 weeks and improved OGTT outcomes at 6 weeks after taurine supplementation in OLETF rats. Taurine significantly reduced insulin resistance (HOMA-IR) but did not improve β cell function (HOMA-β) and islets mass. After 12 weeks, taurine significantly decreased serum levels of lipids such as triglyceride, cholesterol, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C). Taurine significantly lowered serum leptin but not adiponectin levels. However, it did not show its therapeutic effects on the damaged tissues.
Conclusions/interpretation: Taurine ameliorated hyperglycemia and dyslipidemia, at least in part, by improving insulin sensitivity and modulation of leptin in OLETF rats with long duration of diabetes. Further study will be needed to investigate whether taurine has same beneficial effect in diabetic patients.

Preventive roles of taurine in alloxan-induced diabetes

Francoise Sidime, Xin Yan, Lorenz Neuwirth, William L'Amoreaux, Abdeslem El Idrissi

College of Staten Island and Graduate Center, City University of New York, NY 10314, USA

Diabetes Mellitus (DM) is a chronic disease with devastating complications. The hallmark of the disease is high blood glucose level, diabetic neuropathy and retinopathy. In this study we investigate the potential role of taurine in preventing alloxan-induced diabetes. Taurine is a sulphur containing amino acid with several mediate biological processes such as hypoglycemic action, antioxidation, and detoxification. It has been evaluated either in experimental or clinical type 1 and 2 diabetes mellitus and insulin resistance. In this study we evaluated the role of taurine in pancreatic islets development, since the endocrine pancreas undergoes significant modifications during neonatal life. Histological examination of the pancreas from taurine-fed mice revealed a drastic and significant increase in the number and size of the islets of Langerhans. Previously, it has been reported that the islets from taurine treated mice had almost double the number of cells immunopositive for proliferating cell nuclear antigen (PCNA). This increase in proliferation was accompanied by a reduction in the incidence of apoptosis in islet cells. The induction of islet cell apoptosis in vivo involves an increased expression of inducible nitric oxide synthase (iNOS) within β cells. Interestingly, taurine has been shown to be a potent inhibitor of iNOS. We also found a correlate to

the increase in islets size. Taurine-fed mice were hypoglycemic and showed a moderate increase in plasma glucose levels in a glucose tolerance test. Furthermore, taurine-fed mice were resistant to alloxan-induce hyperglycemia. Since the mechanism of alloxan-induced beta cell death is mediate through free radial production and taurine prevent free radical formation, we hypothesize that supplementation of taurine reduces alloxan-induced apoptosis of pancreatic beta cells. This can also be shown by direct injection of cysteamine prior to alloxan injection. Cysteamine is a precursor for taurine biosynthesis and is a free radical scavenger. Cysteamine completely abolished alloxan-induced hyperglycemia through prevention of beta cell apoptosis.

We suggest that the endocrine pancreas undergoes significant modifications during neonatal life and that apoptosis is an important mechanism in this remodeling. Alteration of this remodeling process during this period of time, when a fine balance between cell replication and cell death is critical, would affect the development of the pancreatic islets of Langerhans, and could have important effects on the pancreatic cell mass and the endocrine function and thus diabetes.

Renin-angiotensin system and estrogen attenuates glucose–insulin dysregulation in adult female rats that are perinatally depleted of taurine

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Perinatal taurine depletion followed by high sugar intake (post-weaning) alters renin-angiotensin system and glucoregulation in adult female rats. This study tests the hypothesis that in adult female rats, the renin-angiotensin system and estrogen contribute to insulin resistance resulting from perinatal taurine imbalance. Female Sprague–Dawley rats were fed normal rat chow with 3% β-alanine (taurine deficient, TD), 3% taurine (taurine supplemented, TS) or water alone (C) from conception to weaning. Their female offspring were then fed normal rat chow with 5% glucose in water (TDG, TSG, CG) or water alone (TDW, TSW, CW) throughout the experiment. At 7–8 weeks of age, animals were studied with or without acute inhibition of the renin-angiotensin system by captopril (CW + Cap, CG + Cap, TSW + Cap, TSG + Cap) or estrogen receptors by tamoxifen (CW + Tam, CG + Tam, TSW + Tam, TSG + Tam). All groups displayed similar body, heart, and kidney weights and fasting blood sugars. Compared to CW and CG, perinatal taurine depletion but not supplementation slightly increased plasma insulin levels. High sugar intake slightly increased plasma insulin only in TSG. Surprisingly, captopril treatment significantly increased plasma insulin in all groups except CG (the greatest increase was in TDG). Changes in insulin resistance (HOMA1-IR) and insulin secretion (HOMA1-%B) paralleled the changes in plasma insulin levels. In contrast, tamoxifen treatment had minimal effects on plasma insulin, except in TDG, in which it significantly increased insulin resistance. Also the TDG + Tam group displayed decreased beta cell function related to the control, hyperglycemia, and glucose intolerance. These data indicate that both the renin-angiotensin system and estrogen can attenuate glucose-insulin dysregulation in adult female rats that are perinatally depleted of taurine.

Taurine affects release of insulin and GABA in Hit-T15 β cell line via calcium flux

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Taurine has been shown to be efficacious in altering plasma glucose levels, presumably through release of insulin. In vivo, a rise in plasma glucose concentrations >2.8 mM is sufficient to stimulate the release of insulin from large dense-core vesicles. These vesicles also contain the neurotransmitter GABA, which is thought to regulate glucagon release and ultimately insulin release via feedback inhibition. Previously, we demonstrated that in the Hit-T15 cell line of pancreatic β cells 1 mM taurine significantly decreased cytoplasmic insulin and GABA levels as effectively as 3 mM glucose. Cells treated with 1 mM glucose did not have demonstrable decreases in either insulin or GABA. In this study, we again tested the efficacy of 1 mM taurine in promoting exocytosis of large dense-core vesicle content via calcium flux. Cells were treated either with the subthreshold 1 mM glucose, the stimulatory 3 mM glucose, or with 1 mM taurine. Calcium flux was determined by live cell imaging using Fluo-3. We tracked calcium flux over the first 10 min of treatment with either glucose or taurine. Our data indicate that taurine is capable of stimulating exocytosis by altering calcium flux in these cells.

Neuropsychopharmacological actions of taurine

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Taurine is an endogenous amino sulfonic acid that has been shown to be an inhibitory neuromodulator and a neuroprotecting agent. We reported haloperidol and metoclopramide facilitated development of catalepsy by complex modifications of dopamine and glutamate interactions involving over-excitation of glutamatergic transmission. We wondered if chronic haloperidol-treatment would cause neurodegeneration and catalepsy and if such changes would be prevented by taurine. Chronic 100 mg/kg taurine treatment was found to prevent haloperidol mediated catalepsy as well as neuro-degeneration as measured by blockade of catalepsy and a reduction of tyrosine hydroxylase, dopamine levels and an increase in dopamine D-2 and NMDA receptor densities in the basal ganglia following chronic haloperidol administration. Prevention of haloperidol-mediated augmentation of NMDA receptor concentration in the basal ganglia led us to investigate if taurine would diminish glutamatergic transmission by using electrophysiological and receptor binding studies. Taurine inhibited glutamate-stimulated cortical neuronal firing that is mediated by NMDA receptor system in vitro slice preparations and reduced apparent affinity of glycine as well as polyamine-activated calcium channel opening in NMDA receptor system as analyzed by measuring specific (3H)-MK-801 binding to NMDA receptor in the cortical membrane preparations.

The ability of taurine to inhibit NMDA receptor activation suggested that it may have analgesic properties. Several of the postsynaptic glutamatergic receptors that are expressed in dorsal horn neurons are known to be involved in pain perception. Daily treatment

for 9 days of 100 mg/kg/day taurine caused marked reduction in the tail-flick behavior suggesting that taurine may be a valuable analgesic drug. Since taurine diminishes NMDA receptor activity by interacting at the polyamine site, behavioral effects of chronic taurine treatment was assessed in the force swimming and open field tests to determine if taurine would induce antidepressant-like effects similar to ketamine. We observed that chronic taurine treatment significantly reduced immobility time compared to the saline group, without affecting locomotor activity, suggesting it is an effective antidepressant drug. Although the value of a synthetic derivative of taurine, acamprosate, in the management of drug addiction is well recognized, there is little evidence for anti-addicting properties of taurine. Therefore, we conducted some preliminary experiments on the effects of taurine on cocaine-induced sensitization of locomotor activity and development of conditioned place preference. Daily taurine administration at 100 mg/kg for 5 days was found to be effective in inhibiting the effect of 15 mg/kg (for 5 days) cocaine on locomotor sensitization, suggesting that taurine may have anti-addicting.properties. Daily 15 mg/kg injections of cocaine also significantly induced the development of the acquisition of place preference after an eight-day habituation protocol. The psychomotor stimulant when co-administered with daily 100 mg/kg intraperitoneal (i.p.) taurine failed to develop conditioned place preference suggesting that taurine may be an effective anti-addicting drug. Finally, 100 mg/kg of five daily injections of taurine markedly inhibited dopamine release as measured by microdialysis in the nucleus accumbens, in response to an acute i. p. administration of cocaine (10 mg/kg). The latter effect of taurine may be the mechanism by which it inhibits cocaine-induced addiction. In conclusion, our studies indicate that taurine may be an effective neuro-protective agent, having anti-cataleptic, analgesic, antidepressant, and anti-addicting properties.

Direct interaction of taurine with the NMDA glutamate receptor sub-type via multiple mechanisms

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Taurine, 2-amino-ethanesulfonic acid, is one of the two most abundant free amino acids in the mammalian central nervous system. Taurine is an inhibitory neuro-modulator and protects neurons from glutamate-induced excitotoxicity either by decreasing the intracellular levels of free $Ca2^{+}$ or by opposing the actions of glutamate at its ionotropic or metabotropic receptor sub-types. Several mechanisms for taurine-mediated antagonism against glutamate have been identified including a taurine-activated Cl-influx into different types of neurons that was shown to be blocked by picrotoxin, suggesting that tuarine's action may occur through activation of the GABA-a receptor. Yarbrough and associates (1981), however, identified and described 6-aminomethyl-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide as a specific antagonist against taurine that does not modify GABA-a- or glycine-receptor mediated Cl- channel activation. In addition, taurine was found to inhibit veratridine-stimulated release of (3H)-aspartate from mice corticostrital slices, and that was reported to be antagonized by the omission of Cl- or addition of picrotoxin in the incubation medium. Therefore, taurine may oppose glutamate-induced excitotoxicity by increasing Cl-influx either at a presynaptic site by suppressing glutamate's release or at postsynaptic sites by antagonizing actions on intracellular $Ca2^{+}$ levels.

No previous investigator has reported a direct interaction of taurine with the glutamate NMDA receptor. Here we demonstrate direct interactions of taurine with the NMDA receptor by using electrophysiological recording and receptor binding studies in the rat prefrontal cortical slice and well-washed membrane preparations. Layer-5 neuronal population response (field potential) in the medial prefrontal cortex evoked by electrically stimulating the medial ventral cortical area with single pulses was recorded. Picrotoxin (80 μM) was present in all experiments including controls in order to prevent opening of chloride channels gated by GABA or taurine at pre- and post-synaptic sites. This evoked field potential consisted of 2 negative waves, N1 and N2, separated by a positivity P1. Using specific antagonists NBQX and AP-5, we found that N1 was mediated by the AMPA/kainate receptor, while P1 and N2 were mediated by NMDA receptors. Our work to further differentiate possible subtypes of NMDA receptors mediating P1 and N2 is in progress. Taurine at 0.1–10 mM concentration markedly suppressed the amplitude of the N2 evoked-response component (42% suppression by 2 mM taurine), but had no effect on N1, indicating an interaction with the NMDA but not the AMPA/kainate receptor. Taurine also lacked an effect on P1 and early N2 components, suggesting selective actions on specific subtypes of the NMDA receptor. Taurine failed to inhibit specific binding of (3H) MK-801 to rat cortical membrane preparations in the presence of 30 μM glycine, but 0.1 mM taurine decreased by about 20% the spermine-induced enhancement of specific (3H) MK-801 binding. Furthermore, 0.1 mM taurine diminished the apparent affinity of NMDA receptor to glycine by about 10-fold in the presence of 0.1 mM spermine. Thus, our results indicate that taurine may oppose the actions of glutamate by several novel mechanisms through directly interacting with the NMDA receptor sub-type and these effects of taurine may play a critical role in its neuro-protective actions.

Metabotropic effect of taurine regulation of potassium channels via 5-HT2A serotonin receptors

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Taurine is one of the most abundant amino acids in the CNS and plays a critical role in many physiological functions including neurodevelopment, mentor health and antioxidation. However, the mechanism underlying taurine's action has yet to be determined. In the retinal neurons, we show a metabotropic taurine response that was insensitive to tradition Cl-channel inhibitors, picrotoxin and strychnine, but inhibited by a specific serotonin receptor 5-HT2A antagonist, MDL11939. The metabotropic taurine effect activated intracellular PKC-mediated pathways that consequently increased the delayed rectifier K+ channel currents in the retinal action potential neurons. This study provides an insight into understanding a basic mechanism and the therapeutic value of taurine in the CNS.

Perinatal taurine exposure affects patterns of autonomic nerve activity in adult male rats

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Perinatal taurine excess or deficit influences adult health and disease, especially relative to the autonomic nervous system. This study tests the hypothesis that perinatal taurine exposure influences the adult autonomic nervous system control of arterial pressure in response to acute electrical tooth pulp stimulation. Female Sprague–Dawley rats were fed normal rat chow with 3% β-alanine (taurine depletion, TD), 3% taurine (taurine supplementation, TS) or water alone (Control, C) from conception to weaning. Their male offspring were fed normal rat chow and tap water throughout the experiment. At 8–10 weeks of age, blood chemistry, arterial pressure, heart rate and renal sympathetic nerve activity were measured in anesthetized rats. Age, body weight, mean arterial pressure, heart rate, plasma electrolytes, blood urea nitrogen, plasma creatinine, and plasma cortisol were not significantly different among the three groups. Before tooth pulp stimulation, low (0.3–0.5 Hz) and high frequency (0.5–4.0 Hz) power spectral densities of arterial pressure were not significantly different among groups, while the power spectral densities of renal sympathetic nerve activity were significantly decreased, but only in TD when compared to control groups. Tooth pulp stimulation did not change arterial pressure, heart rate, renal sympathetic nerve and arterial pressure power spectral densities in the 0.3–4.0 Hz spectrum or renal sympathetic nerve firing rate in any group. In contrast, perinatal taurine imbalance disturbed very low frequency power spectral densities of both arterial pressure and renal sympathetic nerve activity (below 0.1 Hz), both before and after the tooth pulp stimulation. The power densities of TS were more sensitive to ganglionic blockade and central adrenergic inhibition, while those of TD were more sensitive to both central and peripheral adrenergic inhibition. The present results indicate that perinatal taurine imbalance can lead to aberrant autonomic nervous system responses in adult male rats.

Effects of acute vs. chronic taurine treatment on context fear aversive conditioning in mice

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Taurine when given acutely is anxiolytic, whereas chronic treatment produces anxiogenic phenotypes under behavioral test conditions. The induction of hyperexcitability under chronic taurine treatment is further exacerbated under stress-induced testing and thus compromises discriminative aversive learning. In the present study, we further investigated the differences in taurine treatment in the 3 day context fear test to elucidate differences under aversive conditioning. Mice learn to anticipate the aversive foot shock through freezing in response to the conditioned cues, including the context of the test chamber. On day 2 mice were presented with the same cues, no foot shock, to measure learning retention of the aversive conditioning 24 h later. On day 3 the context of the test chamber was physically altered and an olfactory cue was added to assess the retention of the context and sound cue conditioning versus potential generalization of stress into subsequent novel environments. Our data revealed that after 4 trials of aversive conditioning acute taurine mice froze 26.81% less than controls, whereas chronic taurine mice exhibit 23.05% increased freezing. On day 2, in the context alone control, acute and chronic taurine mice exhibited a 6.4% reduction, 13.77% increase, and 58.40% reduction respectively in freezing behavior. Once the cues were presented (i.e. no foot shock) control mice had a 31.08% increased freezing response. Interestingly, both taurine treated mice freezing responses did not increase from context conditioned levels when presented with the cues absent of foot shock. This suggests that taurine, in both treatments, evoked equal yet maximal fear responses to the non-aversive cues, but differed only when the aversive stimuli were presented. On day 3 when presented with the altered context acute and chronic taurine mice exhibited a 39.22 and 37.06% higher freezing response than controls in the novel environment, but there were no taurine differences. Similarly, mice freezing response to the tone in the altered context under acute (27.98% increase) and chronic (34.25% increase) taurine treatment did not differ. Our data suggests that stress-induced taurine differences, either acute or chronic, have opposing aversive conditioning profiles. Consistent with our previous findings, we suggest that acute taurine exposure produces less fear and increased inhibition, whereas chronic taurine exposure produces increased fear and decreased inhibition to aversive stimuli. Interestingly, once aversive learning is evoked mice become hypersensitive to novel environments. Taurine levels in the brain have been suggested to increase in response to stressors as a neuroprotective mechanism to prevent hyperexcitability. However, chronic taurine supplementation increases the accumulation of cysteamine, which in turn, depletes somatostatin expression resulting in disregulation of fear inhibition through GABAergic projection neurons in the amygdala and periaquaductal gray; thus, resulting in the exaggerated freezing response observed in our study. These effects are not seen with acute taurine exposure. These findings suggest that taurine causes not only varied phenotypic profiles of emotional fear induced learning, but are further complicated by the inability to associate cues with aversive stimuli due to potential sensory overloading.

Neuro-protective mechanism of taurine—role of endoplasmic reticulum

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Taurine is one of the most abundant amino acids in mammals and is especially enriched in electrically excitable tissues such as the brain, retina, heart, and skeletal muscles. Taurine has been implicated in a variety of functions such as an anti-inflammatory molecule, osmolyte, anti-oxidant, trophic factor, as a neurotransmitter/neuromodulator and a neuro-protective agent. Taurine has been used with varying degrees of success for the treatment of a variety of conditions, including, but not limited to, cardiovascular diseases, hypercholesterolemia, epilepsy, macular degeneration, Alzheimer's disease, hepatic disorders, alcoholism, cystic fibrosis, neurodegenerative diseases and, most recently in vitro fertilization. The mechanism of neuro-protective function of taurine is multi-facet involving minimally modulating the mitochondrial pore permeability, attenuating the endoplasmic reticulum (ER) stress, maintaining calcium homeostasis, and down-regulating the activities of a range of pro-apoptotic proteins, including calpain and caspases, while up-regulating a variety of anti-apoptotic proteins such as Bcl-2 family. In this communication, we will focus on the role of taurine in modulating the ER stress. Factors such as oxidative stress, calcium overload, accumulation of mis-folded proteins all can trigger ER stress leading to over expression of ER stress proteins e.g., Grp78 which further activates Ire1, PERK and ATF6 signaling pathways resulting in the up-regulation of C/EBP homologous protein (CHOP) and DNA damage inducible protein 153 (GADD 153). Taurine is effective in reducing the ER stress in a number of systems that we have studied including the PC12 cell cultures, primary neuronal cultures and human neuroblastoma cell

lines. In summary, taurine exerts its neuro-protective function in part by restoring the integrity of the structure and function of the ER since in the presence of taurine the level of the expression of a number of ER stress proteins including Grp78, CHOP/GADD153, p-IRE-1, and p-eIF–2alpha proteins, caspase-12, the ratio of cleaved ATF6 and full length ATF6 and the ratio of Bax/Bcl-2 is greatly reduced. (Supported in part by grant from James & Esther King Biomedical Research Program, State of Florida and the Neuroscience Research Priority grant, Florida Atlantic University).

Taurine exerts robust protection against hypoxia and glucose deprivation in human neuroblastoma cell culture

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Stroke is one of the leading causes of mortality and disability worldwide. There is no effective intervention for stroke despite extensive research. Taurine is a free amino acid which is present in high concentration in a range of organs including the brain, heart, retina etc. in mammals. It has been shown that taurine can significantly increase the cell survivals under stroke conditions in both in vivo and in vitro models. Recently, we have found that several agents including granulocyte colony-stimulating factor (G-CSF), a stem cell enhancer and facilitator; *S*-methyl-*N*,*N*-diethylthiolcarbamate sulfoxide (DETC-MeSO), a NMDA receptor partial antagonist; sulindac, a potent anti-oxidant, and taurine, a neuroprotective and calcium regulator are effective in protecting stroke induced neuronal injury when it was used alone or in combination either in the animal model or in the tissue/cell culture model. For animal model, we used the middle cerebral artery occlusion (MCAO) rat stroke model. In the MCAO model, the blood flow in the cerebral artery is typically reduced to about 40% of the control and the duration of ischemic condition is for 90 min. For the tissue/cell culture model, we used the primary neuronal cultures, PC 12 cultures and human neuroblastoma cell cultures. In the culture model, the oxygen level is typically reduced from 21 to 0.3% and the duration of hypoxia is for 24 h. We found that in the MCAO animal model, all the neuroprotective agents tested as mentioned above reduced the infarct size ranging from 40 to 60% based on 2, 3, 5-Triphenyltetrazolium chloride (TTC) staining on brain slices either 4 or 8 days after MCAO surgery compared to the control group. In cultures model, they all suppresses the up-regulation of Endoplasmic Reticulum (ER)stress markers and pro-apoptotic markers induced by hypoxia and glucose deprivation, suggesting that they may exert a protective function against hypoxia and glucose deprivation by reducing the ER stress and the apoptotic pathways. A model representing the mode of action of these neuroprotective or neuroregenerative agents in reducing stroke/hypoxia-induced neuronal injury will be presented. (Supported in part by James & Esther King Biomedical Research Grant # 09KW-11).

Changes in gene expression at inhibitory synapses in response to taurine treatment

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Taurine, 2-aminoethanesulfonic acid, is one of the most abundant free amino acids especially in excitable tissues, with wide physiological actions. We have previously reported that in mice, supplementation of the drinking water with taurine induces alterations in the inhibitory GABAergic system. In taurine-fed mice we found that the expression level of glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis, is elevated. Increased expression of GAD was accompanied by increased levels of GABA. In this study we performed qRT-PCR to investigate changes in mRNA expression of various subunits of the $GABA_A$ receptors and GAD65. Consistent with the western blot data and immunohistochemistry, we found that the mRNA for $\beta 3$ subunit was decreased and the mRNA for GAD65 was increased and this increase in gene expression was global throughout the brain. Interestingly however, we found that other subunits of the $GABA_A$ receptors mainly $\beta 1$ and $\beta 2$ were increased. Since the $GABA_A$ is a pentameric receptor and each subunit is encoded by a separate gene, we hypothesize that this differential gene expression of the various subunits of the $GABA_A$ receptors could be a compensatory mechanism to increased excitability and subunit composition of the $GABA_A$ receptors in response to taurine treatment.

Lethality of taurine and alcohol co-administration in 7 day-old, adult and old mice

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Alcohol consumption of mothers during pregnancy causes fetal alcohol syndrome associated with massive neuronal apoptosis. Acute exposure of developing rodents to alcohol causes likewise extensive apoptotic neurodegeneration throughout the brain. In our research we used 7 day-old mice as a model of fetal alcohol syndrom in humans. Using activated caspase-3 and TUNEL staining as markers of the apoptotic process we demonstrated that taurine at a dose of 2 g/kg saves in 7 day-old mice about 50% of dying neurons in the external and internal layers of the cerebellum from ethanol-induced apoptosis. In an attempt to rescue more neurons we increased the taurine dose two- and threefold. Ethanol (20% w/v solution) was administered subcutaneously at a total dose of 5 g/kg (2.5 g/kg at 1 h and 2.5 g/kg at 3 h). Taurine (7% solution) was injected in two half-doses (first at 0 h and second at 4 h). Opposite to our expectations the increased taurine doses administered to ethanol-injected mice induced death. The dose of 4 g/kg co-administered with ethanol killed 50% of mice and the dose of 6 g/kg killed them all. All mice treated with ethanol or taurine alone survived. We repeated the same regime in adult (5–6 months) and old (12–13 months) mice with different doses of ethanol and taurine injected intraperitoneally. The co-administration of taurine at a total dose of 10 g/kg with ethanol (8 g/kg) killed 100% of adult mice. In the old mice the lethal dose was 6 g/kg of taurine co-administered with 6 g/kg of ethanol. All adult and old mice treated with taurine or ethanol alone survived. The adult and old mice treated with ethanol and taurine showed a marked fall in the blood glucose level before their deaths. No changes occurred in the blood glucose level in mice which received only taurine or ethanol. We assume that the drop in blood glucose after the taurine and ethanol co-administration can be one reason of lethality. Comparison of the lethal doses

of taurine and ethanol co-administration in 7 day-old, adult and old mice allows us to conclude that the adverse effects of taurine and ethanol combined toxicity is age-dependent. Our present findings are an important warning sign of the interactions of taurine and ethanol and their combined toxic effects, particularly for young people mixing taurine-containing energy drinks with alcohol. This research was supported by the competitive research funding of Pirkanmaa Hospital District and Finnish Foundation for Alcohol Studies.

The mechanism of taurine protection against endoplasmic reticulum stress in stroke related conditions in primary neuronal cell culture

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Taurine is a free amino acid and is one of the most abundant amino acids present in mammalian nervous systems. Taurine has been shown to provide protection against neurological diseases, such as Huntington, Alzheimer's diseases and stroke. Stroke especially the ischemic stroke is one of the leading causes of death and disability in the world. It is generally believed that ischemia-induced brain injury is largely due to excessive release of glutamate resulting in excitotoxicity and cell death. Despite extensive research, there is still no effective intervention for stroke. Recently, we have shown that taurine can provide effective protection against endoplasmic reticulum (ER) stress induced by excitotoxicity or oxidative stress in PC12 cell line or primary neuronal cell cultures. In this study, we used hypoxia/reoxygenation condition in primary cortical neuronal cultures as a model for stroke. We found that when primary neuronal cultures were first subjected to hypoxic conditions where the oxygen level was kept at 0.3% for 24 h, followed by re-oxygenation where the oxygen level was maintained at 21% for 24–48 h, the cell viability was greatly reduced and ER stress markers, caspase-12, GADD153/CHOP GRP78, CHOP, p-IRE-1, and p-eIF-2alpha proteins, were markedly increased. Furthermore, we found that under the same hypoxia/reoxygenation condition as mentioned above taurine greatly increased the cell viability as measured by ATP assay and inhibited the up-regulation of caspase-12 and GADD153/CHOP induced by hypoxia/reoxygenation, suggesting that taurine may exert a protective function against hypoxia/reoxygenation by reducing the ER stress. Moreover, taurine can down-regulate the ratio of cleaved ATF6 and full length ATF6, and p-IRE1 expression, indicating that taurine inhibits the ER stress induced by hypoxia/reoxygenation and glutamate through suppressing ATF6 and IRE1 pathways. (Supported in part by James & Esther King Biomedical Research Grant # 09KW-11).

Regulation of taurine release by neurotransmitter receptors

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Taurine release from nervous cells can be mediated by simple leakage through membranes, reverse action of taurine transporters, flux through anion channels and exocytosis. Calcium dependency is assumed to witness the exocytotic release of transmitters from synaptic vesicles. The question of calcium dependency of stimulated taurine release is not yet settled. The stimulated taurine release may originate from calcium-dependent emptying of synaptic vesicles or directly from cytoplasma. Different neurotransmitters have been shown to affect taurine release. The activation of all ionotropic glutamate receptors evoke taurine release from different brain preparations in vitro and also in the brain in vivo. The receptor antagonists block or markedly attenuate the agonist-induced release. The activation of *N*-methyl-D-aspartate (NMDA) receptors leads to activation of the nitric oxide (NO)/cyclic GMP (cGMP) cascade which pathway enhances taurine release. The effects of metabotropic glutamate receptors are markedly variable, both enhancing and attenuating effects being seen, depending of the receptor group and brain preparations subjected to studies. In general, the group II agonists potentiate markedly and group III agonists slightly taurine release. These effects are blocked by the antagonists. The group I agonists have been only marginally effective or not effective at all. Taurine release has been concentration-dependently potentiated by γ-aminobutyrate (GABA), which effect is blocked by GABAA-receptor antagonists, whereas GABAB receptor agonist tend to inhibit taurine release. Activation of adenosine A1 and A2 receptors have also enhanced taurine release in some brain preparations. On the other hand, taurine reciprocally affects the release of both excitatory and inhibitory neurotransmitters. It does thus occupy a pivotal role in the balance between excitation and inhibition in the brain.

Differential regulation of TauT by vitamin D3 and retinoic acid via VDR/RXR in LLC-PK1 and MCF-7 cells

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Background: The interaction between taurine and the absorption of fat-soluble vitamins, such as vitamins A and D, has been an interesting topic in the field of nutrition science because taurine-conjugated bile acids optimize fat and fat-soluble vitamin absorption. However, whether the hormone calcitriol (1,25-dihydroxyvitamin D3) and retinoic acid regulate the expression of the TauT gene is unknown. In this study we test the hypothesis that the TauT gene is regulated by vitamin D3 (VD3) and retinoic acid (RA) via activation of a vitamin D receptor (VDR) and a retinoic acid receptor (RXR).
Methods: Taurine uptake, Western blotting, gene reporter assay and immunohistochemical analysis of TauT, VDR, and RXR were used in VD3 and/or RA treated LLC-PK1 and MCF-7 cells.
Results: In the present study we demonstrated that VD3 alone had little effect on TauT expression in both LLC-PK1 and MCF-7 cells. Expression of TauT was significantly increased by RA, which was synergized by the addition of VD3 after RXR activation in LLC-PK1 cells. In contrast, expression of TauT was significantly decreased by the combination of VD3 and RA in MCF-7 cells. Regulation of TauT by VD3/RA appears to occur at the transcriptional level, as determined by a reporter gene assay of the TauT promoter. Immunohistochemical study showed that VDR and RXR were activated by VD3 and RA, respectively, in both LLC-PK1 and MCF-7 cells. The activated VDR and RXR also co-located in the nuclei of both cells, suggesting that there is a VDR/RXR complex involved in the transcriptional regulation of TauT.
Conclusion: Our results show that expression of TauT is differentially regulated by VD3 and RA via formation of a VDR and RXR complex in the nuclei in a cell type-dependent manner.

Reduced placental taurine transporter (TauT) activity in pregnancies complicated by maternal obesity and pre-eclampsia

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Taurine is conditionally essential in human pregnancy as cysteine sulphinic acid decarboxylase, which catalyses taurine synthesis, is not expressed by fetal tissues. Both the fetus and placenta require taurine for normal growth and development. This demand is met by taurine uptake from maternal blood into syncytiotrophoblast, the transport epithelium of the placenta, through the activity of TauT on the maternal-facing plasma membrane. Pre-eclampsia and maternal obesity are complications of pregnancy associated with fetal growth restriction, dysregulation of syncytiotrophoblast renewal, placental nitrative stress and elevated adipo- and inflammatory cytokines. Maternal obesity increases the risk of pre-eclampsia although the reasons for this are poorly understood. We tested the hypothesis that syncytiotrophoblast TauT activity is reduced in maternal obesity and pre-eclampsia compared to women of ideal weight having normal pregnancy and explored regulation of placental TauT activity by adipocytokines.

To investigate maternal obesity, body mass index (BMI) was recorded at the first antenatal visit and women grouped as ideal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) or obese (class I 30–34.9; class II 35–39.9; class III = 40). In a separate study, women with pre-eclampsia (blood pressure >140/90 mmHg in previously normotensive women plus proteinuria) were compared with women having uncomplicated pregnancy. Syncytiotrophoblast TauT activity was measured as the Na+-dependent uptake of 3H-taurine into placental villous tissue fragments over 30–120 min (pmol/mg tissue protein).

TauT activity at 120 min was inversely related to maternal BMI (linear regression $p < 0.05$; $n = 74$) and was significantly lower (27% reduction) in obese class III ($n = 9$) than ideal weight women ($n = 23$; $p < 0.01$; Mann–Whitney). Syncytiotrophoblast TauT activity was also lower in pre-eclampsia ($n = 6$) than in normal pregnancy ($n = 5$) ($p < 0.05$; Mann–Whitney). Western blotting of membrane enriched placental samples from obese women (class III; $n = 6$) or women with pre-eclampsia ($n = 8$) showed no difference in TauT expression compared to ideal weight women having normal pregnancy. Thus syncytiotrophoblast TauT activity, but not expression, is reduced in maternal obesity and pre-eclampsia.

To investigate whether syncytiotrophoblast TauT activity is down-regulated by adipocytokines that are elevated in maternal obesity and pre-eclampsia, placental villous fragments of normal pregnancy were maintained in explant culture (7 days) and treated for 48 h (days 5,6) with leptin (50/500 ng/ml) or IL-6 (2/20 pg/ml). Neither leptin nor IL-6 altered TauT activity measured in explants at day 7. In contrast, exposing explants to phorbol 12-myristate-13-acetate (1 μM for 3 h) to activate protein kinase C (PKC), reduced TauT activity by 22% ($n = 5$; $p < 0.05$ Wilcoxon signed rank test).

Reduced placental TauT activity in maternal obesity and pre-eclampsia could contribute to fetal growth restriction and dysregulated syncytiotrophoblast renewal that is common to both these pregnancy complications. In several non-placental tissues TauT is inhibited by nitration and PKC-induced phosphorylation and we are exploring the possibility that nitration of TauT and/or activation of PKC down-regulates syncytiotrophoblast TauT activity in maternal obesity and pre-eclampsia.

Knockdown of TauT expression impairs human embryonic kidney 293 cell development

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Heller-Stilb et al. have demonstrated that TauT deficiency results in small kidneys in TauT knockout mice. Our studies have shown that TauT is a direct target of several genes, including p53 and WT1, that play an important role in renal development. However, whether the TauT gene is directly involved in renal development is largely unknown. In the present study we created a TauT-deficient cell model by RNAi in human embryonic kidney 293 cells and the effect of TauT on renal development was investigated. Knockdown of TauT significantly decreased the growth rate, cell migration, and colony formation of 293 cells. Inhibition of TauT caused cell cycle G2 arrest. Microarray analysis showed that several genes that are involved in cell cycle regulation or cell division, such as CDK6 and CDC7, were significantly down-regulated in TauT-deficient 293 cells as compared to control 293 cells. In conclusion, the results from this study suggest that TauT plays a role in the development of renal cells. Knockdown of TauT impairs kidney development, possibly through regulation of cell cycle-related genes.

Gestational taurine availability and fetal programming of metabolism in C57BL/6 mice

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Gestational protein restriction induces fetal programming resulting in decreased taurine levels in dams and fetus, low birth weight, and insulin resistance and type 2 diabetes in adulthood. Taurine supplementation of dams protects against these effects.

We asked whether or not the decrease in taurine alone could account for these effects by supplying a taurine uptake inhibitor, guanidine–ethanesulfonic acid (GES) (2% w/v in the drinking water), during gestation of C57/BL6 mice. Furthermore we examined if gestational GES changed the response of the adult offspring to a high fat diet.

GES caused a 12% decrease in birth weight ($p < 0.001$). The decrease in weight was persistent until 3 months of age.

At 3 months of age, GES-females, but not GES-males had decreased fasting glucose ($p = 0.0002$) with no difference in fasting insulin. Remarkably, GES-females showed a deterioration in glucose tolerance ($p = 0.02$), whereas GES-males showed an improvement ($p = 0.03$).

At 6 months of age, after 3 months on a HFD, there was no longer a difference in body weight between GES and control, but the GES-females had an increased fat pad weight ($p = 0.003$). Furthermore, no difference in glucose tolerance was observed at 6 months.

In conclusion, low taurine availability during gestation has a gender-specific fetal programming effect on glucose homeostasis when on a chow diet. The fetal programming effect disappears following a high-fat diet.

Taurine and mitochondrial bioenergetics

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The very high concentration of taurine in oxidative tissue has recently led to discussions on the role of taurine in the mitochondria, e.g. with taurine acting as pH buffer in the mitochondrial matrix.

The current biochemistry textbook presentations of mitochondrial function focus on the chemiosmotic theory with its subsequent proton gradient and oxidative phosphorylation, including introduction of the tricarboxylic acid cycle and the electron transport chain.

However, will it be reasonable to include taurine in such traditional presentation of mitochondrial oxidation? What modifications and clarifications of the model will be needed to display and understand the role of taurine?

Consequently, a careful review of mitochondrial oxidation is needed to identify the key elements and processes that taurine can enhance or stabilise.

Taurine and fish nutrition: where do we stand on the use of this mythical molecule?

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Aquaculture is a recent food production sector that has rapidly grown in the last 50 years. In the period 1970–2008, the production of fish from aquaculture increased at an average annual rate of 8.3%. Aquaculture is the fastest-growing animal-food-producing sector, accounting for almost half of total food fish supply. Nutritional research plays a pivotal role in fish culture to optimise growth rates and feed efficiency, contributing to the economic success of the activity and guarantying minimal environmental impacts. Furthermore, it is well know from the producers of this sector the importance of producing healthy fish, guarantying a high quality product for the consumer and reducing the associated costs of malpractices. In this sense, in the last years, taurine has come to fish nutritionist's attention and several studies have been done using this mythical molecule as a dietary supplement. However, the results were sometimes contradictory and, most importantly, several questions have arisen. For instance, it is still not clear if fish are able to synthesise taurine and the mechanisms leading to growth enhancement are still poorly understood.

In a time when these and other questions are still under investigation by fish nutritionists, another challenge has been imposed to the aquaculture industry, especially to fish producers, in a way that taurine assumed an even more remarkable place in nutritional fish research. In recent years, the pressure to replace fishmeal in fish diets has seriously increased. This is due not only to the increasing price of this diminishing resource but also as a result of consumer's demand to grow fish in an environmentally friendly and sustainable way that reduces its dependence on fisheries products. Thus, research on alternative protein sources for fish feeds has increased, with an emphasis on terrestrial plant proteins. However, when large amounts of dietary fishmeal are replaced by plantmeal, lower fish growth, poorer physiological condition or reduced feed efficiency are usually observed. Among other factors, these negative effects may result from a taurine deficiency, which is virtually absent in plants but is particularly abundant in fish. In this way, research on alternative protein sources for fish feed has exponentially increased and some of these studies have focused on the use of taurine as a way to overcome part of the problems identified.

Therefore, this presentation intends to review how taurine has been used by fish nutritionists along the last decades and how new challenges imposed to the aquaculture industry increased research on the effects of taurine supplementation to plantmeal based diets. Results from our own research team on this subject will be highlighted and new ideas and future trends pointed out. This review will help to clarify how a holistic knowledge on the physiological importance of taurine and on the mechanisms that lead to the optimisation of growth and feed efficiency in fish is clearly missing, being paramount towards a sustainable aquaculture growth.

The physiological role of taurine during fish development—relevant aspects for the aquaculture industry

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The aquaculture industry has grown more rapidly than any other food-producing sector, increasing from less than one million tonnes in early 1950s to more than 50 million tonnes nowadays. However, the evolution of this industry has been hindered by a poor understanding of fish nutritional requirements during larval stage, when the digestive tract is poorly differentiated with a limited absorption capacity. Therefore, comprehending fish larval nutritional physiology will ultimately lead to a successful production of high quality juveniles in marine fish aquaculture.

A recent focus of aquaculture nutritionists has been the physiological role of taurine during fish development. Like several mammal species, the ability to biosynthesise taurine varies among fish species and along ontogenesis. Although positive effects for dietary taurine supplementation have been demonstrated for fish juveniles, few works have considered fish larvae where dietary taurine deficiencies may be particularly critical. On one hand, high taurine levels found during egg and yolk-sac stage suggest a high physiological importance of taurine for the fish early life stages. Furthermore, the prey of fish larvae in natural environment contains high taurine levels, unlike the feed usually provided during larval rearing. In addition, dietary taurine supplementation has been shown to increase growth in several larval fish species reared under intensive conditions, suggesting that fish larvae should feed upon taurine enriched diets.

In this study, three experiments were conducted to further explore the physiological role of taurine during fish development. Two model species were used: gilthead seabream (*Sparus aurata*) and the flatfish Senegalese sole (*Solea senegalensis*), a dominant and an emerging species for aquaculture in Southern-European countries, respectively. Firstly, the effect of dietary taurine supplementation was assessed on growth and methionine metabolism of seabream larvae. Secondly, the effect of dietary taurine supplementation was evaluated based on growth, metamorphosis success and amino acid metabolism of sole larvae. Finally, the expression of taurine transporter (TauT) was characterised by qPCR in sole larvae and juvenile tissues.

Results showed that dietary taurine supplementation did not increase seabream larval growth, possibly because this species seems to be able to biosynthesise taurine from methionine during the larval stage, not relying on a dietary source of taurine to maintain the taurine

body pool. However, dietary taurine supplementation significantly increased sole larval growth, metamorphosis success and amino acid retention, indicating that this supplementation may be beneficial for flatfish larvae. Results also showed that metamorphosis is an important developmental trigger to promote taurine transport in sole larval tissues. In sole juveniles, TauT expression was highest in brain, heart and eye, organs where taurine is reported to play important biological roles and is found in high concentrations. Moreover, a high TauT expression found in juvenile hindgut tissues suggests an enterohepatic recycling pathway for taurine in sole, a process that may be important to maintain taurine body levels in flatfish species. Hence, this work show how different fish species differ on their dependence on dietary taurine and highlights the vital role of taurine for development of flatfish, an extremely valuable group targeted by the aquaculture industry.

The ability of taurine as a marker for the identification of natural Calculus Bovis and its substitutes

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Purpose: *Calculus Bovis* (: *C. Bovis*) is one of the most famous animal derived therapeutic preparations in Japan and China. Although a source of Bos Taurus is quite rare in nature, there is increased therapeutic demand for the preparation. In China, two artificial substitutes for Bos Taurus are available; one is artificial *C. Bovis*, a mixture of bile salts, bilirubin, taurine and some undetermined ingredients. The other is in vitro cultured *C. Bovis*, produced in vitro under conditions mimicking in vivo gallstone formation. Previously, we proposed potential differences between natural *C. Bovis* and its substitutes. To verify our hypothesis, we both investigated the biological differences between the preparations and established methodology to distinguish between natural *C. Bovis* and its substitutes.
Methods: We prepared 9 samples of natural *C. Bovis* from various countries and 4 samples of substitutes from China; 2 samples of artificial *C. Bovis* and two samples of in vitro cultured *C. Bovis*. To evaluate the biological activity of *C. Bovis*, we examined viability of primary cultured cardiac fibroblasts prepared from 1 day old Wistar rats. We also compared inorganic and organic ingredients of the samples by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Liquid Chromatography (LC), respectively.
Results: Cardiac fibroblasts treated for 1 h with 25 mg/ml of *C. Bovis* substitutes experienced a reduction in viability, as detected by the MTS assay. On the other hand, 25 mg/ml natural *C. Bovis* from Australia lacked cytotoxicity. Based on ICP-MS analysis, the Fe, Mg and Ca composition of the substitutes was higher than that of natural *C. Bovis*. Moreover, LC analysis revealed that the substitutes contained more cholic acid than the natural preparation. Indeed, about 80% of the bile acid pool consisted of cholic acid in two batches of in vitro cultured *C. Bovis*. Furthermore, artificial *C. Bovis* and in vitro cultured *C. Bovis* prepared according to accepted manufacturing methodology contained about 30–850 mmol/g taurine. By contrast, most natural *C. Bovis* contains <5 mmol/g taurine. Finally, differences in spectroscopic analyses (coherent transition radiation from LINAC and Mössbauer spectrometry) were detected between natural *C. Bovis* and its substitutes.
Conclusion: The present results reveal biological differences between natural *C. Bovis* and its substitutes. Because the substitutes appear to be supplemented with taurine and other compounds, the supplements may serve as markers to distinguish between natural *C. Bovis* and its substitutes

Effect of arsenic on the expressions of thyroid hormone receptor genes in mice brains and protection of taurine

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Purpose: To exploring effect of arsenic (As) on expressions of thyroid hormone receptor (TR) genes and protection of taurine.
Methods: The SPF mice were randomly divided into three As exposure groups, one protective group and one control group. The As exposure groups were administered with 1, 2 and 4 ppm As_2O_3, respectively through drinking water for 60 days. The protective group was treated with both 4 ppm As_2O_3 and 150 mg/kg taurine. The control group was given with drinking water alone. The gene expressions of TRa1 and TRβ in the mice brains of the five groups were analyzed by real time PCR. Their protein expressions were examined by Western blot.
Results: Our results showed that expression of TRβ, a very important regulator of Camk4 transcription was down-regulated in cerebral and cerebellar tissues of mice exposed to As. However, there were no significant differences in the gene expressions of TRa1 between the As exposure groups and controls. We further analyzed the influence of As on expressions of TRa1 TRβ1 and TRβ2 proteins in brain by Western blot. The quantity of TRβ1 band in the cerebral or cerebellar tissue significantly decreased in the groups exposed to As compared to the control group, agreeing well with results by the real time PCR. Furthermore, The expression of TRβ gene and TRβ1 proteins was significantly rescued in the group coadministered with taurine as antioxidant.
Conclusions: Subchronic exposure to As impedes the TRβ1 expression and taurine prevents from the down-regulation of TRβ1 by As. These results indicated that The TRβ1 may be a target of As-induced neurotoxicity via Camk4-regulation pathway and that taurine has protection against As-induced neurotoxicity.
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Posters

Monoaminergic activity is increased following electroconvulsive therapy (ECT), but less is known about amino acids

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Background/aim: Taurine has been shown to be elevated in the plasma and lymphocytes of depressed patients, but its level

normalises after successful drug therapy. This study was performed to examine taurine levels in depressed patients before and after ECT.
Methods: Twenty-three patients undergoing ECT were recruited. Fasting blood samples were collected before the first and after the third ECT treatments. The severity of depression was estimated with the Montgomery-Asberg Depression Rating Scale (MADRS) at the time of blood sampling. We analyzed the levels of taurine in plasma.
Results: After three ECTs, a decrease in MADRS scores was found for the entire group ($p = 0.0001$). Simultaneously, the mean plasma taurine level was reduced from 59.5 ± 16.0 μmol/L before the therapy to 53.3 ± 11.8 μmol/L after three ECT administrations ($p = 0.01$). The decrease in the plasma taurine levels was significant for the responders ($n = 7$; $p = 0.03$) but not for the non-responders ($n = 16$; $p = 0.09$).
Conclusions: Plasma taurine levels decrease significantly after three ECT treatments in patients who respond to treatment. The results indicate that taurine may play a role in the pathophysiology of depression.

Synthesis of carbohydrate–taurine derivatives

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It is generally believed that taurine plays an enantiostatic role in response to external perturbations. In order to improve the effectiveness and selectivity in the biological actions, some kind of modification is necessary on the taurine moiety. The chemical syntheses and physiological studies of carbohydrate-taurine derivatives are not well documented in the literature. As a part of the project for the establishment of carbohydrate-taurine library, several carbohydrate–taurine derivatives such as 1-deoxy-1-(sulfoethylamino)-D-frutose was prepared in a very convenient way from D-hexoses. Suitably protected D-hexoses or D-ketoses were reacted with taurine to afford carbohydrate–taurine adduct, which was subjected to Amadori rearrangement to give ketose–taurine derivative. The reaction conditions and syntheses of some other carbohydrate–taurine derivatives will be presented.

The effect of bisphosphonates drug and hyperglycemic condition on taurine transport at inner blood–retinal barrier

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Diabetic retinopathy (DR) is result from angiogenesis in the retina as a complication of diabetes. Recently, bisphsphonates (BP), anti-osteoporosis agents, have been reported to have anti-angiogenic effect. We studied to elucidate the effect of BP on taurine transport at the inner blood–retinal barrier (iBRB) in high glucose condition and normal. Taurine transport at iBRB was determined by measuring the uptake of [3H]taurine using a conditionally immortalized rat retinal capillary endothelial cell line (TR-iBRB cells). As a result, pre-treatment of alendronate increased [3H]taurine uptake. But in high glucose medium condition and treatment of cyrochalasin B, taurine uptake was reduced about 20% of normal condition.

Taurine tissue concentrations in metabolic disease measured by a cheap enzyme based assay

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Several links have been made between altered metabolism of the β-amino acid taurine (2-amino-ethanesulfonic acid) and development of type 2 diabetes (T2D), as well as between taurine supplementation and prevention of diabetes and diabetic complications. However, the effect of T2D on taurine metabolism in tissues has so far remained largely unknown, and research in this area has been hindered by the costs and difficulties of measuring taurine levels in many tissue samples.

Here we present the development of a cheap, enzyme based assay for measuring taurine content in serum/plasma and various tissues in a 96-well plate format. The assay utilizes the *E. coli* α-ketoglutarate dependent enzyme taurine dioxygenase (TauD), which catalyzes the conversion of taurine to sulfite. In reaction with TauD, taurine levels are measured spectro-photometrically using Ellman's Reagent (5,5′-dithiobis-(2-nitrobenzoic acid or DTNB), which produces a yellow product in reaction with sulfite.

Using the developed assay, we established base line taurine levels in liver, skeletal muscle, heart, kidney, pancreas, adipose tissue, brain, and plasma from of 8 week old male Wistar rats.

Moreover, we examined taurine homeostasis during development of T2D by measuring taurine levels in plasma and tissues from the following rodent models of obesity, insulin resistance, and T2D: Goto Kakizaki (GK) rats (6 and 16 weeks old), Zucker diabetic fatty (ZDF) rats, high-fructose fed Wistar rats, high-fat fed Wistar rats, high-fat fed C57/BL6 mice, and db/db mice.

The effect of taurine on glucose and lipid homeostasis in fructose-fed Wistar rats

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The non protein amino acid taurine has been shown to counteract the negative effects of a high fructose diet in rats with regard to insulin resistance. The effect may involve taurine interaction with insulin signal transduction resulting in increased glucose uptake thereby preventing insulin resistance. Furthermore, taurine has been shown to ameliorate fructose induced dyslipidemia. Here we examined both the long-term (26 weeks) and short-term (7 weeks) effects of oral taurine supplementation (2% in the drinking water) in fructose-fed Wistar rats.

In the long-term study, taurine improved glucose tolerance, but also increased fasting glucose levels. Taurine had no effect upon fasting insulin levels or homeostasis model assessment of insulin resistance (HOMA-IR). Likewise, no effect of taurine upon hepatic and plasma triglyceride levels or on plasma free fatty acid levels was observed. Taurine had no effect on in vivo insulin induced phosphorylation of Akt in skeletal muscle.

In the short-term study, taurine had no effect upon lipid parameters and glucose tolerance, but increased both fasting insulin and

HOMA-IR when given in combination with fructose. Furthermore, taurine had no effect upon glucose uptake in isolated skeletal muscle.

In conclusion, the study suggests that long-term taurine supplementation improves glucose tolerance. However, the study did not corroborate findings showing that taurine improved fructose induced dyslipidemia. Furthermore, as taurine increased fasting glucose levels, the beneficial effect of taurine supplementation towards amelioration of insulin resistance is questionable.

Comparative evaluation of the efffects of hypotaurine, taurine and thiotaurine on alterations of the cellular redox status and activities of antioxidant and glutathione-related enzymes by acetaminophen in the rat

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In an early study we demonstrated that the sulfinate hypotaurine (HYTAU) and sulfonate taurine (TAU) were able to protect the rat liver against hepatocellular damage, lipid peroxidation and the loss of activities of enzymes participating in glutathione redox cycling, utilization and synthesis as a result of an acute exposure to a hepatotoxic dose of acetaminophen (APAP). Furthermore, these sulfur-containing compounds where shown to be about equipotent as *N*-acetylcysteine (NAC), the antidote of choice for APAP poisoning. The aim of the present investigation was to determine the impact that the thiosulfonate functional group, as found in thiotaurine (TTAU), could have on APAP-related oxidative stress, impairment of the activity of glutathione-related enzymes, and activities of hepatic antioxidant enzymes. To this end, male Sprague–Dawley rats, 225–250 g, were intraperitoneally treated with a 2.4 mmol/kg dose of a sulfur-containing compound (HYTAU, TAU or TTAU), followed 30 min later by an 800 mg/kg dose of APAP. A reference group received 2.4 mmol/kg of NAC prior to APAP. Naive rats served as controls. At 6 h after APAP, the animals were sacrificed by decapitation, their blood collected into heparinized tubes, and their livers immediately removed by the freeze clamp technique. Aliquots of liver were made into 1:20 homogenates in Tris buffer pH 7.0 containing phenylmethylsulfonyl fluoride (most assays) or in 25% metaphosphoric acid–phosphate buffered saline pH 8.0 (1:5, glutathione and glutathione disulfide assays). Plasma and liver samples were assayed for contents of malondialdehyde, reduced glutathione and glutathione disulfide; and for activities of catalase, glutathione peroxidase, superoxide dismutase, glutathione reductase, glutathione *S*-transferase and glutathione synthetase. APAP increased lipid peroxidation, lowered the reduced/disulfide glutathione ratio and the activities of all enzymes tested, especially those of antioxidant enzymes. In general, all sulfur-containing compounds were effective in ameliorating the biochemical alterations caused by APAP, with HYTAU and TTAU usually providing a protection that was equipotent with each other and often greater than that by TAU. On the other hand, the effects of NAC were rather similar to those by HYTAU and TTAU both in scope and magnitude. In short, sulfinate and thiosulfonate analogs of TAU appear to be somewhat more effective than TAU in counteracting APAP-induced oxidative stress and changes in the activities of enzymes associated with glutathione redox cycling, utilization and synthesis both in the liver and plasma. Moreover, these TAU analogs were as effective as NAC, the antidote of choice for acetaminophen poisoning.

Effects of dietary taurine supplementation on serum taurine and adipokine level in diet-induced obesity rat model

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Adipose tissue is known to release a variety of adipokines including leptin and adiponectin. The purpose of this study was to investigate the effect of dietary taurine supplementation on the development of obesity in diet-induced obesity rat model. Five week-old male Sprague–Dawley rats were randomly divided into three groups for a period of 8 weeks (normal diet, N group; high fat diet, HF group; high fat diet + taurine, HFT group). Taurine was supplemented by dissolving in feed water (3% w/v), and the same amount of distilled water was orally administrated to N and HF groups. In serum, total cholesterol level was lower in HFT group compared to other groups. Serum adiponectin level was higher in HFT group compared to HF group. The serum taurine level was negatively correlated with final body weight and total cholesterol level and positively correlated with adiponectin level. The leptin level was positively correlated with epididymal and retroperitoneal fat weights and triglyceride level. These results suggest that dietary taurine supplementation has beneficial effects on body weight, total cholesterol level and adiponectin level in diet-induced obesity rat model.

Effects of taurine on iNOS-dependent DNA damage in heavy exercise skeletal muscle by inhibiting NF-κB signaling pathway

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Taurine protects against tissue damage in a variety of models involving oxidative stress especially in the exercise. The mechanism of taurine protection is not well understood but the ability of taurine to attenuate the toxic effects of HOCl/OCl by formation of taurine choramine and its subsequent effects are thought to be important. Heavy exercise is thought to increase oxidative stress and damage muscle tissue. Nitrosative stress-mediated activation of inflammatory mediators is currently being emphasized as an important factor involved in inflammation-related disorders. Nitrosative stress arises mainly from the large accumulation of NO by the overexpression of iNOS in the damaged tissue to form peroxynitrite ($ONOO^-$) when NO reacts with the superoxide anion (O_2^-) and form 8-nitroguanine. The aim of this study was to determine the taurine cytoprotective role on the nitrosative stress in the intense exercise-induced skeletal muscle damage.

We set up a heavy exercise bout protocol for rats consisting of climbing ran on a treadmill and examined the effect of intraabdominal administration of taurine at 1 h before heavy exercise at a dose of 5 mg/kg/day for 10 consecutive days. Each group ran on the treadmill at 20 m/min, 25% grade, for 20 min or until exhaustion within 20 min once for 10 days. Exhaustion was determined as the point when an animal was unable to right itself when placed on its side. The muscle damage was associated with an increase accumulation of 8-nitroguanine and 8-oxodG in the nuclei of skeletal muscle

cells. The immunoreactivities for NF-κB, iNOS are also shown increase in the exercise group. Taurine treatments group significantly ameliorated heavy exercise-induced muscle DNA damage as revealed by reduce the accumulation of 8-nitroguanine and 8-oxodG, possibly through downregulating the expression for reduction iNOS by modulation of NF-κB activation.

In conclusion, the present study demonstrates for the first time that taurine exhibits protective effects against intense exercise-induced nitrosative DNA damage in the skeletal muscle of rats. Taurine treatments significantly prevent iNOS expression, indicating that nitrosative stress raised by heavy exercise could be modulated by taurine. Upregulated expression of iNOS in skeletal muscles could be responsible for the nitrosative muscle damage induced by heavy exercise, probably by modulating inflammation-mediated damage on the NF-κB signaling pathway.

Taurine and adipokines level in 8 week body weight control program in obese female college students

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Human adipose tissue is not only a storage organ but also an active endocrine organ to release adipokines, e.g., adiponectin, leptin, and homocystein. This study was conducted to investigate serum taurine level and adipokines level in 8 week body weight control program in Korean obese female college students (n = 18). The program was consisted of diet therapy, exercise, and behavior modification. Body composition, serum lipid profiles, serum taurine, adiponectin, leptin, and homocystein level were assessed before and after the program. Differences between before and after the program were analyzed with paired t test (SPSS version 15.0). Average age and height was 20.8 ± 0.4 years old and 162.0 ± 1.0 cm. After the program, body weight, percent body fat, BMI were significantly decreased. Also serum triglyceride, total cholesterol, and LDL-cholesterol levels were significantly decreased. Serum adiponectin level was significantly increased and leptin level was significantly decreased. There were no differences in changes between before and after the program regarding serum taurine or homocystein level. The change of percent body fat was negatively correlated with serum adiponectin level. These results may suggest that percent body fat loss by body weight control program is associated with an increase in serum adiponectin in obese female college students. Therefore, an intervention study is needed about correlation between dietary taurine intake and serum adipokines or taurine level.

Evaluation of taurine as anti-alopecia agent using *C. elegans*

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Alopecia (loss of hair) has been considered as a modern disease which is caused by stressful conditions. Major cases of alopecia were found among individuals of 40–50s; nowadays, even among the 20–30s. This study characterized taurine's potential against alopecia caused by chemical stress agent, singularly or in mixture with other anti-alopecia agents such as Astressin-B, Biotin, Capsaicin, and Finasteride. The criteria used are the expression of stress markers and measurements of movement, lifespan comparison, and offspring number. *C. elegans* showed the typical stress symptoms under treatment with stress agent. Evidently, hsp-70 protein expression increased while worms' lifespan and per capita offspring number significantly decreased along with a remarkably lowered movement. A positive response was shown when worms were treated with astressin-B, biotin, capsaicin, and finasteride. Among the singular treatment, Astressin-B showed the better outcomes with Biotin the least in terms of stress-reducing effects. The single treatment with taurine was comparable to that of Astressin-B. Synergistic effect was best shown in the treatment with Biotin and taurine. In conclusion, a strong proof was shown that taurine has a great potential as anti-alopecia effect especially against the one caused by stresses. In addition, the present study implies that the anti-alopecia effect of taurine might be augmented when it was used with other commercially available anti-alopecia agents such as biotin.

Taurine inhibited LPS induced declines in neurogenesis in DG

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Neurogenesis was traditionally believed to occur only during embryonic stages in mammalian CNS, but has been recently reported to occur in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus of adult mammalian CNS. Taurine demonstrates multiple cellular functions including a central role as a neurotransmitter, as a trophic factor in CNS development, in maintaining the structural integrity of the membrane, in regulating calcium transport and homeostasis, as an osmolyte, as a neuromodulator and as a neuroprotectant. And taurine level in the brain was reported to significantly increase under stressful conditions, suggesting that taurine may play a vital role in neuroprotection. The present study aimed to elucidate the effect of taurine on neurogenesis in the DG of adult rats under the condition of acute Lipopolysaccharide (LPS) administration which is a bacterial endotoxin released during infection and is known to suppress neurogenesis in the dentate gyrus (DG) in mature rats. Rats in Taurine and LPS + Tau groups were intraperitoneally injected with taurine (200 mg/kg) for 39 days, while rats in Saline and LPS + Saline groups were intraperitoneally injected with the same volume of saline. Internal jugular vein cannulation was performed 1 week prior to a single injection of Brdu (200 mg/kg) simultaneously with LPS (1 mg/kg) or saline injection. Blood samples were collected 2 h after LPS injection for TNF-α and IL-1β detection. All rats were sacrificed 24 h after LPS injection and brains were collected for Brdu, ki67 and Iba-1 immumohistochemical examination. The results showed that taurine could significantly inhibit the decrease of the number of Brdu and Ki67 positive cells in the SGZ of hippocampus 24 h after LPS injection but had no significant difference compared with the control group, suggesting that taurine could protect against LPS induced declines in neurogenesis, but exerted no effects on neurogenesis of normal rats when under the present condition. Effects of LPS on microglia were observed at 24 h after LPS injection. Iba-1 positive cells were significantly higher in rats treated with LPS, while animals

treated with taurine could inhibit the increase of Iba-1 positive cells, and there is no significant difference between taurine groups and saline group. The serum concentration of TNF-α and IL-1β 2 h after LPS injection were significantly increased, which was significantly decreased by taurine administration. The results indicated that taurine could effectively protect against LPS induced declines in neurogenesis by inhibiting the increase of microglia and cytokines especially TNF-α and IL-1β, as for the effects of taurine on neurogenesis in normal rats, maybe higher concentration and longer duration are needed, which should be detected in the future research.

Characterization of anti-stress effect of taurine on plant cells cultured in vitro

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Taurine is shown to reduce physiological stress in many types of animal cells. Although taurine may work similarly in plant cells, it was not well characterized as an anti-stress agent in plants. This study characterizes taurine's potential anti-stress effect in sweet potatoes, Ipomoea batatas. Tunicamycin was used to alter physiological conditions. Taurine's effect, as anti-stress agent, was characterized according to assays of shoot and root generation. Shoot was scored daily and the time taken up to the shoot appearance was compared between taurine and non-taurine treatment. Root regeneration was scored on the daily basis after callus fragments were placed on the basal media. Visual comparison was also performed on the two different treatments. The anti-stress effect was evident in the taurine treated plant tissue. With increasing amount of taurine, the extent of shoot generation greatly enhanced. In terms of duration leading to shoot generation, taurine-treated callus generated shoots faster than the non-taurine treated counterpart. The time reduction in the shoot generation appeared greater in a dose-dependent manner. Taurine also exerted a positive effect on root induction of the nascent shoots which were placed on the root inducing media or basal media. Roots were formed more rapidly than the stressed controls. In conclusion, these results strongly imply that taurine plays an important role in overcoming physiological stresses in plant along with animal cells. Taurine can be used to lessen a physiological stresses and future related research may be very meaningful to investigate taurine as a potential anti-stress agent against drought, air pollution, and oxidative stresses in plants.

The effects of chronic taurine supplementation on motor learning

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It has previously been shown that chronic taurine supplementation in drinking water results in several biochemical changes in the inhibitory GABAergic system. The brains of mice chronically treated with taurine have alterations in the GABAergic system, which is consistent with hyperexcitability. Desensitization of the inhibitory system is seen following chronic taurine treatment, primarily through $GABA_A$ receptors. This is believed to occur because mice undergoing chronic treatment may have elevated extracellular taurine concentrations, which would lead to a down regulation of $GABA_A$ receptor function or expression. A down regulation of $GABA_A$ receptor expression might be due to a sustained interaction of taurine with $GABA_A$ receptors. This process would then decrease the efficacy of the inhibitory synapses at the postsynaptic membrane. If changes occur in the GABAergic system as a possible compensatory mechanism due to taurine administration, then it is important to study all aspects by which taurine induces hyperexcitability, and affects behavior. We hypothesized that modification of the GABAergic system in response to taurine supplementation influences motor learning capacity in mice. To test this hypothesis, the rotarod task was employed after chronic taurine supplementation. The rotarod is an apparatus which is used to gauge the ability of an animal to maintain balance on a rotating rod. Experiments were carried out on FVB/NJ adult male mice. Animals were given either distilled water ($n = 3$), and served as controls, or a solution of 0.05% taurine dissolved in distilled water ($n = 3$). After 4 weeks of chronic taurine supplementation these animals were then subjected to behavioral experimentation. Analyses were performed using Statistica V 6.1 (Statsoft, Inc. Tulsa, OK). Multifactorial analysis of variance was used in order to study the interaction effects among treatments. Results from this study suggest that there may be differences in the underlying structure and/or function of the brain regions involved in rotarod performance after chronic taurine supplementation. Our data show that chronic taurine supplementation may have contributed to motor learning deficits. The taurine-fed mice displayed minor improvements after repeated training when compared to controls. Also, during the testing session the taurine-fed mice exhibited a shorter latency to fall, as the task requirements became more demanding.

Taurine enhances anticancer activity of cisplatin in human cancer cells

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Taurine is a non-essential amino acid and has a variety of physiological and pharmacological effects. Taurine is found in high concentrations in the white blood cells, skeletal muscles, central nervous system and heart muscles. Recently, protective effects of taurine against anticancer drugs on normal cells were investigated. But anticancer effects of taurine on cancer cells remain poorly understood. Therefore, we investigated the anticancer effects of taurine in human cancer cells. In co-treatment of cisplatin with taurine, cell proliferation was more decreased than single treatment of cisplatin. Reduced cell proliferation was caused by cell cycle disruption. Therefore cisplatin and taurine were treated for 72 h, cell cycle was analyzed. Co-treatment of cisplatin with taurine leads to cell cycle arrest. Taurine is known to have antioxidant effects. Therefore we investigated the ROS level. The result was interesting that taurine enhanced cisplatin-elevated ROS level. Moreover co-treatment of cisplatin with taurine had influence on ROS-related enzyme. In present study, the results indicated that co-treatment of cisplatin with taurine was more effective than single-treatment of cisplatin.

Effects of taurine on male sexuality in rats

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It has been demonstrated that taurine is abundant in male reproductive organs, and can be biosynthesized by testis. The levels of luteinizing hormone (LH) and testosterone (T) were found to be obviously increased by taurine supplementation in rats of different ages in our previous study, which indicated that taurine may have some effects on male sexuality. The primary aim of the present study was to investigate the effect of taurine on male sexuality in rats. Taurine was offered in water to male adult (10 weeks old) and aged (20 months old) rats for 2 months. The effect of taurine on the level of nitric oxide synthase (NOS) and nitric oxide (NO) in serum, and male sexuality were investigated. The results showed that the level of NOS was obviously increased, but the levels of NO were significantly decreasedby taurine administration in adult rats, While the levels of NOS and NO were both significantly elevated by taurine administration in aged rats. Taurine can significantly increase the numbers of erection, mounting and ejaculation, obviously decrease the latent periods of erection and catching in old rat, but has no significant effects on adult rats. The results indicated that taurine may play an important role in male sexuality, especially in old rats by improving the level of NOS and NO, the exact mechanism of which need to be further investigated.

Protective effect of taurine on tri-ortho-cresyl phosphate (TOCP) induced cytotoxicity in C6 glioma cell

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Tri-ortho-cresyl phosphate (TOCP) an organophosphorus ester can cause neurotoxicity via oxidative stress pathway. Taurine is an antioxidant. The objective of this study was to investigate the protective effect of taurine on TOCP induced cytotoxicity in C6 glioma cell. The cultured cells were pretreated with 0, 1, 3, 9 mM of taurine for 30 min prior to 1 mM TOCP treatment. After 48 h, the glioma cell survival was determined by3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyltetrazolium bromide (MTT) assay and lactate dehydrogenase (LDH) release. The activities of GPx and the content of GSH were also analyzed by kits. Our results showed that survival of the glioma cells decreased in the group treated with TOCP alone and increased in the groups pre-treated with taurine significantly in a concentration-dependent manner. TOCP induced decrease in the activity of glutathione peroxidase (GPx) and the content of glutathione (GSH). However, taurine prevented these decreases. Our results suggested that taurine has protective effect on TOCP-induced toxicity to glioma cells via elevating antioxidant capacity.

Evaluation of taurine levels in plasma and aqueous humour from normal domestic dogs: a pilot study

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Taurine is an amino amino which plays a critical role in retinal degeneration. Indeed, plasmatic taurine depletion was incriminated in the retinal toxicity induced by the antiepileptic drug vigabatrin, which leads to the degeneration of retinal ganglion cells (RGCs), and can be prevented by taurine supplementation. More recently, we found that taurine supplementation also prevents the retinal ganglion cell degeneration in different models of glaucoma. Accordingly, the evaluation of taurine levels could be a crucial parameter which may detect a retinal vulnerability. Because a lot of breeds of dog can develop glaucoma pathologies, we performed taurine measurements on plasma and aqueous humor (AH) samples from domestic dogs.

Here, we exposed results from a pilot study on 71 "normal" dogs without ocular pathologies. Samples were collected by veterinarians who belong to the "Réseau Européen d'Ophtalmologie Vétérinaire et de Vision Animale" and taurine measurements were performed using HPLC techniques.

In a first stage of samplings, we found that plasmatic levels was 148.8 ± 5.9 μM (mean ± SEM) in a cohort of 39 dogs collected by eleven veterinarians. No differences between sexes were observed. However, one group of dogs presented a plasmatic taurine level significantly higher (385.2 ± 16.6 μM, $n = 5$; $p < 0.001$). Interestingly, in this latter group, dogs had a non standard diet as compared to the other groups that suggests the direct impact of nutrition on plasmatic taurine level in dogs. In a second stage, we found a plasmatic taurine amount very similar as the one measured in the first stage (141.8 ± 13.2 μM, mean ± SEM, in a cohort of 25 dogs collected by 4 veterinarians). For this second cohort, we also measured the taurine level in AH. We found the presence of taurine in AH at the concentration of 51.8 ± 5.0 μM (mean ± SEM; $n = 10$). No correlation was observed between the taurine amounts in plasma and aqueous humor.

This pilot study indicates that the plasmatic taurine amount is ~150 μM in "normal" domestic dogs. We also detected taurine amounts in AH with a concentration of ~50 μM. Interestingly, plasmatic taurine levels seem to change in dogs according to their diet. Additional data will need to confirm if taurine-enriched diet can increase taurine amounts in plasma and AH. Moreover, further studies will determine if taurine amounts from glaucomatous dogs are changed in plasma and AH.

Effect of dietary taurine and arginine supplementation on bone mineral density in growing female rats

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The purpose of this study was to determine the effect of arginine or taurine alone and taurine plus arginine on bone mineral density and markers of bone formation and bone in growing female rats. Forty female SD rats (75 ± 5 g) were randomly divided into four groups (control, taurine, arginine, taurine + arginine group) and treatment lasted for 9 weeks. All rats were fed on a diet and deionized water. Bone mineral density (BMD) and bone mineral content (BMC) were measured using PIXImus (GE Lunar Co, Wisconsin, USA) in spine and femur. The serum and urine concentrations of calcium and phosphorus were determined. Bone formation was measured by serum osteocalcin and alkaline phosphatase (ALP) concentrations, and the bone resorption rate was measured by deoxypyridinoline (DPD) crosslinks. Femur BMD was significantly increased in the group with

taurine supplementation and femur BMC/weight was significantly increased in the group with arginine supplementation. Rats fed an arginine or taurine supplemental diet increased femur bone mineral density or femur bone mineral content, but a taurine + arginine supplemented diet does not have a better effect than arginine or taurine alone. The results of this study suggest that taurine or arginine supplementation may be beneficial on femur BMD in growing female rats. Additional work is needed to clarify the interactive effects between the taurine and arginine to determine whether dietary intakes of arginine and taurine affects on bone quality in growing rats.

Effect of taurine feeding on bone mineral density and bone markers in the rat

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The purpose of this study was to investigate the effect of dietary taurine supplementation on bone mineral density (BMD) and bone mineral content (BMC) in rats. Twenty Sprague–Dawley male rats(-body weight 200 ± 10 g) were divided into two groups, control and taurine group (2% taurine supplemented diet).

All rats were fed on experimental diet and deionized water and libitum for 6 weeks. Serum alkaline phosphatase activity (ALP), osteocalcin, PTH and urinary deoxypyridinoline (DPD) crosslinks value were measured as markers of bone formation and resorption. Bone mineral density (BMD) and bone mineral content (BMC) were measured using PIXImus (GE Lunar Co. Wisconsin) in spine and femur. The effect of diet on ALP, Osteocalcine, and PTH were not significant. There were no significant differences in ALP, osteocalcine, and PTH concentration. Urinary calcium excretion was lower in taurine group than in control group. Femur BMC/weight of taurine group was significantly higher than control group. The results of this study show that the possible role of taurine to bone metabolism in male rats.

The role of taurine on the skeletal muscle cell differentiation

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Background/aim: Taurine contained abundantly in the skeletal muscle has been considered as one of essential factors for the differentiation and growth of skeletal muscles. The previous studies in the taurine transporter (TAUT) knockout mice showed that deficiency of taurine caused incomplete muscular development and exercise abilities. In fetal and neonatal periods, taurine must be an essential amino acid due to no biosynthesis capacity, and therefore, taurine should be endogenously supplied through placenta and milk. Although muscular taurine content is much higher in the slow twitch fiber type (Type I) than in the fast twitch fiber type (Type II), muscle cell differentiates firstly from embryonic type to Type II. The present study examined the role of taurine treatment on the differentiation of mouse myoblast to myotube.
Method: Confluent mouse differentiable C2C12 cell was cultured with ~20 mM taurine in a differentiation medium for up to a week with/without silencing of taurine transporter gene (taut), transport competitor; β-alanine, Ca2+ chelator; nifedipine, or calcineurin inhibitor; FK506. The expressions of differentiation markers were evaluated by RT-qPCR, fluorescence immunohistochemical stain, or Western blot. Furthermore, the gene expressions of myosin heavy chain (MHC) type were measured during differentiation period with taurine.
Result: The differentiation to myotube was significantly and dose-dependently enhanced by taurine treatment, in particular 6-fold in 20 mM taurine, estimated by fusion index and maximal diameter in the MHC-positive myotubes. The phosphorylations p38 MAPK were decreased by taurine. The enhanced differentiations by taurine were significantly cancelled by the taut silencing, beta-alanine, nifedipine, or FK506. Myh4 (Type IIB) gene but not Myh1 (IID/X) and Myh2 (IIA) was increased by taurine treatment for a week.
Conclusion: Exogenous taurine might play a key role for the mature differentiation/growth on the skeletal muscle during development period. This result conceives that taurine might contribute the recovery from muscle damages and differentiation of satellite cells.

Taurine chloramine increases HO-1 expression and activity by promoting Nrf2 activation via oxidative modification of Keap1

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Taurine chloramine (TauCl) is produced by a reaction between taurine and the HOCl produced by myeloperoxidase in neutrophils. TauCl has been shown to increase heme oxygenase (HO)-1 expression and HO activity in macrophages. In this study, we learned that TauCl increased HO-1 expression and HO activity in RAW 264.7 macrophages by increasing nuclear translocation of NF-E2-related factor 2 (Nrf2) and its binding to antioxidant response element (ARE) as well as cytosolic content of Nrf2. However, the activation of other transcription factors like NFκB, AP-1 and CREB was not altered in the TauCl treated macrophages. The knock down of Nrf2 expression by transfection of its siRNA reduced the TauCl-induced HO-1 expression. TauCl decreased the content of biotin-PEAC5-maleimide-bound Keap1 and appeared to increase the oxidation of Keap1. In summary, TauCl produced abundantly by activated neutrophils lead to increase HO-1 expression and HO activity in macrophages by increasing Nrf2 expression and its nuclear translocation and ARE binding. TauCl promotes the oxidative modification of Keap1 and enhances nuclear translocation of Nrf2 that results in the elevation of HO activity required for efficient removal of free-heme in cells undergoing oxidative stress.

Taurine has no effect on inhibition of human adipocyte differentiation and change of adipokine expression in adipocyte induced by endoplasmic reticulum stress

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Background: In obesity and diabetes, adipocyte show significant endoplasmic reticulum (ER) stress. Hyperglycemia-induced ER stress has not been studied on the adipocyte differentiation and adipokine expression. Taurine has been known to protect the cells against ER stress. This study examined the effect of taurine on ER stress induced adipocyte differentiation and adipokine expression.

Methods: Human preadipocytes into adipocytes was differentiated in the presence or absence of taurine under ER stress condition. Change of adipokine expression in adipocyte stimulated by IL-1β was investigated in the presence or absence of taurine.
Results: Thapsigargin (10 nM) or high glucose concentration (100 mM) as ER stress inducer was treated during the differentiation of human preadipocyte to adipocytes. Thapsigargin inhibited the differentiation of adipocyte in dose dependant manner but the treatment of high glucose concentration did not. Taurine treatment (100 mM) did not block the inhibition of differentiation of preadipocyte to adipocyte. Furthermore, the treatment of high glucose concentration inhibited the expression of adiponectin and increased the expression of leptin in human adipocytes. However, taurine treatment did not affect the expression of two adipokines.
Conclusions: Taurine may not affect the inhibition of adipocyte differentiation and the change of adipokines expression in human adipocytes under ER stress, even though taurine has known to show the protective effect on ER stress-induced cells.

Free radical scavenging activities of taurine by electron spin resonance spectrometry

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Taurine may play an important role in protecting cells against toxic injury by an antioxidant. However, there is a lack of evidence to support this hypothesis. The objective of this study was to examine the in vitro antioxidant properties of taurine against different reactive species at various concentrations. The radical scavenging effects of taurine on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, hydroxyl radical, superoxide radical and alkyl radical were investigated using a spin-trapping electron method and compared with the electron spin resonance (ESR) signal intensity. ESR assays showed that DPPH radical scavenging activity of taurine at various concentrations (0.03125 $\sim$ 1 mg/mL) was elevated with a decrease of ESR signals in a dose-dependent manner. Moreover, taurine exhibited the radical scavenging activities against hydroxyl radicals, superoxide radicals, and alkyl radicals. Findings from this study suggest that taurine may be a useful radical scavenger and a potential supplement for the food, pharmaceutical, and cosmetic industries as well as feed and/or antibiotic because of its potent antioxidant capacities against various reactive radicals.

Taurine promotes glucose uptake in cultured rat skeletal L6 myotubes

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Taurine (2-aminoethanesulfonic acid), a sulfur-containing β-amino acid, is found in all animal cells at millimolar concentrations and has been reported to show various health promoting activities including anti-diabetic properties. The beneficial effects of taurine in diabetes mellitus have been known. However, the exact mechanism of hypoglycemic action of taurine is not properly defined. In the present study, we investigated anti-diabetic effect of taurine in the cell culture system using rat skeletal muscle cells. In cultured rat skeletal L6 myotubes, we studied the effect of taurine (0 $\sim$ 100 μM) on glucose uptake to plasma membrane from the aspects of AMP-activated protein kinase (AMPK) signaling. Taurine stimulated glucose uptake in a dose-dependent manner by activating AMPK signaling. From these results, it may suggest that taurine show anti-diabetic effect by stimulating insulin-independent glucose uptake in rat skeletal muscle.

Effects of taurine supplementation upon food intake and central insulin signaling in malnourished mice fed a high fat diet (HFD)

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Background/aims: Feeding behavior is a major determinant of body composition, adiposity and glucose homeostasis. Both obesity and malnutrition are risk factors for the metabolic syndrome and are associated with altered food intake. Here we assessed the effects of TAU supplementation on adiposity, food intake and central insulin signaling in malnourished mice fed a HFD.
Methods: weaned male C57BL/6 mice were fed a control (14% protein-C) or a protein-restricted (6% protein-R) diet. After 6 weeks, both groups received or not HFD for 8 weeks (CH and RH). Half of the HFD groups were supplemented with 5% TAU in their drinking water (CHT and RHT).
Results: Both HFD groups were overweight ($C = 26.60 \pm 0.59$; $CH = 38.66 \pm 1.12$; $R = 20.76 \pm 1.33$; $RH = 29.84 \pm 0.92$ g; $P < 0.05$) and showed increased perigonadal (PG) and retroperitoneal (RP) fat pads [$CH = 4.66 \pm 0.12$ and 1.39 ± 0.08; $RH = 3.21 \pm 0.39$ and 1.17 ± 0.14% body weight (BW), for PG and RP respectively] compared with C or R groups (PG: $C = 1.81 \pm 0.24$; $R = 1.61 \pm 0.29$ and RP: $C = 0.59 \pm 0.10$; $R = 0.52 \pm 0.08$% BW; $P < 0.05$). TAU supplementation attenuated obesity in CHT (BW 33 ± 1.53 g; PG 3.66 ± 0.34 and RP 1.02 ± 0.05% BW) but not in RHT mice (BW 30.45 ± 1.49 g; PG 3.24 ± 0.18 and RP 1.18% BW). HFD induces hypercholesterolemia ($CH = 146.7 \pm 6.55$ and $RH = 142.4 \pm 9.19$ vs $C = 108.2 \pm 11.64$ and $R = 98.27 \pm 10.61$ mg/dL; $P < 0.05$) and glucose intolerance, as assessed by the area under glycemic curves ($C = 20.11 \pm 1.59$; $CH = 30.21 \pm 2.30$; $R = 15.45 \pm 1.58$; $RH = 27.44 \pm 2.40$ mg/dL min^{-1}), although fasting hyperglycemia was seen only in CH group, with a 44% higher total glucose plasma levels ($P < 0.05$). TAU supplementation improved glucose homeostasis only in CHT group with decrease of 18 and 21% of glucose plasma levels and the area under glycemic curves, respectively. Western blot analysis showed a reduction of 55 and 17% in CH and RH hypothalamic IRS-1(pIRS-1) phosphorylation content at basal conditions compared with C or R groups. TAU treatment increased 35% the Akt activation (pAkt) in CHT without modification in RHT mice. However, supplementation did not alter pIRS-1 content. Together with a lower insulin pathway activation, CH and RH mice presented a higher calorie intake (20.83 ± 0.44 and 19.80 ± 0.64 kcal/day, respectively) related to C

or R mice (C = 15.72 ± 0.50; R = 15.35 ± 0.60 kcal/day; P < 0.05). CHT decreased food intake behavior (17.77 ± 0.89 kcal/day), whereas RHT mice showed a persistent increased food consumption (19.79 ± 0.62 kcal/day).

Conclusions: HFD developed obesity, hypercholesterolemia, glucose intolerance and calorie intake disturbances both in control and malnourished mice. TAU promoted increased hypothalamic insulin action which prevented overfeeding and obesity. Protein-restriction promoted metabolic disturbs that were not restored by TAU supplementation showing enhanced risk to develop metabolic syndrome.

Taurine (TAU) supplementation restores insulin secretion and reduces ER stress markers in protein-malnourished mice

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Background: Endoplasmic reticulum (ER) stress is a cellular response to increased intra-reticular protein accumulation or poor ER function. Chronic activation of this pathway may lead to beta-cell death and metabolic syndrome (MS). Poor nutrition during perinatal period, especially protein malnutrition, is associated with increased risk for MS in later life. Here, we analyzed the effect of TAU supplementation on insulin secretion and protein expression of ER stress markers in pancreatic islets and liver of malnourished mice.

Methods: Weaned male Swiss mice were fed a control (17%-NP) or a low protein (6%-LP) diet for 12 weeks. Half of NP and LP groups were supplemented with 2,5% TAU in their drinking water (NPT and LPT, respectively).

Results: Total body weight (BW) assessed by the area under growth curve in LP mice was significantly lower (LP = 130.1 ± 5.3 g weeks^{-1}) compared with NP mice (200.3 ± 12.2 g weeks^{-1}; P < 0.001). TAU supplementation did not alter BW (NPT = 197.1 ± 11.9; LPT = 146.0 ± 5.3 g weeks^{-1}). Both LP and LPT groups had lower fed plasma insulin levels (LP = 1.49 ± 0.3; LPT = 1.60 ± 0.4 vs NP = 4.12 ± 1.1; NPT = 5.05 ± 0.8 ng/ml). Isolated islets from LP mice secreted less insulin in response to 16.7 mM glucose (LP = 1.49 ± 0.45 and NP = 3.64 ± 0.25 ng/islet/h; P < 0.05). TAU supplementation enhanced insulin secretion in NPT islets (5.65 ± 0.49 ng/islet h) and restored the secretory capacity in LPT to the levels of NP islets (2.72 ± 0.62 ng/islet/h). Western blot analysis in NPT and LPT islets showed a lower expression of ER stress marker CHOP (NPT = 62.2 ± 9.1 and LPT = 36.6 ± 14.4% of NP) related to NP (100 ± 2.5% of NP; P < 0.05). In addition, TAU decreased ATF4 expression in NPT islets (NPT = 67.4 ± 7.3 vs. NP = 100 ± 6.4% of NP; P < 0.05). PERK phosphorylation (p-PERK) and BIP expression were not altered, but a survival marker: Akt (p-Akt) was 59% more phosphorylated in NPT islets compared with NP (P < 0.05). Also, NP islets acutely incubated with 3 mM TAU did not alter pAkt but showed a 216% enhanced ERK1/2 activation (p-ERK1/2) after 90 s. Finally, p-PERK and BIP expressions were higher in the liver of LP (146.7 ± 2.6 and 137.8 ± 10.7% of NP, respectively) compared with NP mice (100 ± 4.5 and 100 ± 5.2% of NP). TAU supplementation lowered these ER stress markers in LPT mice (48.4 ± 9.1 and 61.2 ± 15.4% of NP, for p-PERK and BIP, respectively; P < 0.05).

Conclusions: Insulin secretion is impaired by protein-malnutrition. ER stress markers are activated in liver but not in pancreatic islets of malnourished mice. TAU supplementation increases insulin secretion capacity, islet Akt and ERK1/2 activation and reduces ER stress proteins in pancreatic islets and liver, effects that may enhance beta-cell survival and improved body insulin action.

Behavioral and biochemical studies of antidepressant-like effects of taurine

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Depression is a serious mental disorder that affects approximately 20% of the population in the world. To treat depressive disorders, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been widely used in developed countries. However, there are several reports that SSRIs have some harmful side effects including nausea, anorexia, and headache. Therefore, antidepressants without any severe side effects should be developed to improve quality of life for depressive patients. Diet may be one candidate for the prevention and treatment of depressive disorders. Dietary nutrients should be widely screened for antidepressant-like activity. However, the antidepressant-like effects of nutrients have not yet been clarified. The identification of such nutrients may raise the possibility of treating or preventing depression through dietary regimens.

Taurine, 2-aminoethylsulfonic acid, is one of the most abundant amino acids in the brain. It has various important physiological functions as a neuromodulator and antioxidant. Taurine is expected to be involved in depression such as families that suffer from a hereditary taurine deficiency have a tendency to develop depression; however, knowledge regarding its function in relation to depression is limited.

In this study, we attempted to elucidate the effects of oral taurine administration on antidepressant-like behaviors in rats and depression-related signal transduction in the hippocampus.

In behavioral tests, the taurine-containing diet did not influence behaviors in the open field test. Rats fed a high taurine (HT: 45.0 mmol/kg taurine) diet for 4 weeks (HT4w) showed decreased immobility in the forced swim test (FS) compared to controls. However, rats fed a low taurine (LT: 22.5 mmol/kg taurine) diet for 4 weeks or an HT diet for 2 weeks (HT2w) did not show a significant difference in FS compared to controls. FS is one of major behavioral test in depression study and antidepressant administrated mice and rats showed decreased immobility time in FS.

In biochemical analyses, we focused on the expression of glutamic acid decarboxylase (GAD) 65 and GAD67 in the hippocampus. Usp46 mutant mice show negligible immobility in FS and decreased expression of GAD67 in the hippocampus. However, the expression of GAD65 and GAD67 in the hippocampus was not affected by taurine administration. Next, we focused on several key molecules related to depression in the hippocampus. In the result, the phosphorylation levels of extracellular signal-regulated kinase1/2 (ERK1/2), protein kinase B (Akt), glycogen synthase kinase3 beta (GSK3β) and cAMP response element-binding protein (CREB) were increased in the hippocampus of HT4w and HT2w rats. Phospho-calcium/calmodulin-dependent protein kinase II (CaMKII) was increased in the hippocampus of HT4w rats only. Moreover, no significant changes in these molecules were observed in the hippocampus of rats fed an HT diet for 1 day.

In conclusion, our findings suggest that taurine has an antidepressant-like effect and an ability to change depression-related signaling cascades in the hippocampus.

Additional effects of taurine on the benefits of BCAA intake for the delayed-onset-muscle-soreness and muscle-damage induced by high-intense eccentric exercise

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Background and aim: A high-intensity-exercise causes delayed-onset-muscle-soreness (DOMS) and muscle-damages that disturb continuous and practice of exercise. Although several previous studies have showed the effectiveness of BCAA on the DOMS, the certain evidences have still been under developing. Because taurine has been reported to act as anti-inflammatory and anti-oxidative stress, the present study investigated the hypothesis that taurine might enhance the beneficial effects of BCAA supplement on attenuations of the DOMS and muscle-damages induced by high-intensity eccentric exercise.
Methods: Untrained 36 male volunteers (22.5 ± 3.8 years of age) were assigned to four-groups, and ingested the combination of placebo (P) and active (3.2 g BCAA or 2.0 g taurine): PLCB (P/P), BCAA (BCAA/P), TAU (P/taurine), and COMB (BCAA/taurine) groups, thrice a day, from before 2 weeks to after 4 days of eccentric exercise consisting 6 sets of 5 lengthening actions of the elbow flexors using a dumbbell of 90% of maximal isometric strength. The DOMS and muscle damages were subjectively and objectively evaluated using visual analogue scale (VAS), physical parameters (upper arm circumference [CIR] and elbow joint's range of motion), and blood parameters (creatine kinase, lactate dehydrogenase [LDH], aldolase, and aspartate amino transferase). All experiments were carried out under double-blind method.
Results: Plasma taurine concentration was significantly increased in both taurine supplemented groups after 2 weeks, while BCAA was unchanged by BCAA supplementations. Through the following period, all subjective and objective parameters were better in the BCAA and TAU groups compared to the PLCB group, but in the COMB group were further great. Concretely, VAS score under elbow extension at the following second day was significantly lower in the COMB than the PLCB group, and areas under the curve (AUC) during the period were also the lowest in the COMB group. CIR at the following second and third days and AUC were significantly decreased in the COMB compared to those in the PLCB group. Through the period, all blood parameters were lower in the COMB than other groups, and LDH at the following 1–3 days and AUCs in LDH and aldolase were significantly.
Conclusions: Compared with single or placebo supplementations, the combined taurine supplementation with BCAA improved many subjectively and objectively parameters of DOMS and muscle-damages. Therefore, additional supplementation of taurine to BCAA would be one of useful nutritional strategies for attenuation and prevention of DOMS and muscle-damages after high-intensity exercises.

Thiotaurine prevents apoptosis of human neutrophils: a putative role in inflammation

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Thiotaurine (aminoethylthiosulfonate) is a biomolecule structurally related to hypotaurine and taurine. Thiosulfonates (RSO2SH), including thiotaurine, have been occasionally detected among the products of biochemical reactions involving sulfur compounds. Thiotaurine is a metabolic product of cystine through a transsulfuration reaction involving thiocysteine (RSSH) and hypotaurine (RSO2H). In vitro, thiotaurine, can be readily converted in taurine by hydrogen peroxide. Recently, it has been shown that hydrogen sulfide (H2S), an endogenously generated gaseous molecule, plays relevant signal roles, modulating pathophysiological functions such as inflammatory process. Though desulfuration of cysteine constitutes the main source of H2S in mammals, thiotaurine contains a sulfane sulfur atom that can be released as H2S. It is recognized that either hypotaurine, and taurine, and H2S exert a regulatory activity on inflammatory responses, on the contrary thiotaurine has never been investigated for a bioactivity in inflammation. At this regard, the influence of thiotaurine on human leukocyte spontaneous apoptosis has been evaluated. Neutrophil apoptosis is an important process because it provides a signal for neutrophil removal and because it results in the loss of functional neutrophil responsiveness. Thus, modulation of apoptosis may have a major effect on the inflammatory process. As several studies suggested a critical role of caspase-3 in both spontaneous and Fas receptor-mediated apoptosis in neutrophils, the effect of thiotaurine on spontaneous apoptosis by measuring the caspase-3 activity in cell lysates has been studied. Our results indicate that thiotaurine influences lifespan of human neutrophils by inhibition of spontaneous apoptosis in a dose-dependent manner. To test whether thiotaurine influences human neutrophil responses via H2S-release, inhibition of spontaneous apoptosis by this sulfur compound has been carried out in the presence of glutathione. It is well-known that thiol compounds such as glutathione promote reductive breakdown of thiosulfonates generating H2S and sulfinates. Interestingly, in the presence of 1 mM glutathione a 30% increase in the inhibition of spontaneous apoptosis by 100 μM thiotaurine has been observed.

The metabolic fate of thiotaurine in human neutrophils has been also investigated by HPLC analysis. Human leukocytes generate hypotaurine as the main metabolite of thiotaurine. Furthermore, human neutrophils activated by phorbol 12-myristate 13-acetate (PMA) produce also taurine, the oxidation product of both hypotaurine and thiotaurine.

These results indicate that thiotaurine may exert regulatory effects on inflammation influencing lifespan of human neutrophils, also by releasing H2S. As hypotaurine, taurine and H2S can modulate leukocyte functional responses, it would be worthy to investigate the metabolic and functional interplay between thiosulfonates, sulfinates, sulfonates, and H2S at inflammatory sites.

Correlations between dietary taurine intake, dietary habit score and fatigue in Korea college students

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Taurine has the effect on anti-fatigue in rat and has beneficial effect on exercise-induced fatigue in human. The purpose of this study was to investigate the relationship among dietary taurine intake, dietary habit score and fatigue score in Korean college students. The subjects were 239 college students (142 male and 97 female). A 3 day recall method was used for dietary assessment (2 weekdays and 1 weekend day). Fatigue score was determined using a fatigue questionnaire of 'Subjective symptoms of fatigue test'. The higher fatigue scores indicate heavier fatigue. The average total fatigue score ($p < 0.001$), physical fatigue score ($p < 0.001$), mental fatigue score ($p < 0.01$) and nervous fatigue score ($p < 0.001$) of female students were significantly higher compared to male students. Average dietary intake of taurine in male and female was 102.5 and 98.0 mg/day, respectively. There was no significant difference in dietary taurine intake between male and female students. The average dietary habit scores of "eating meals at regular times" ($p < 0.05$), "eating three meals a day" ($p < 0.05$), "having meals with diverse foods" ($p < 0.05$), and "avoiding eating harmful foods" ($p < 0.05$) were significantly lower in female students compare to male students. There was no significant correlation between fatigue score and dietary taurine intake. However, there was significant negative correlation between total fatigue score and dietary habits scores such as "eating meals at regular times" ($p < 0.05$), "eating foods such as meat, fish, eggs, beans more than 2 times a day" ($p < 0.05$), "eating greenish yellow vegetable every meals" ($p < 0.05$), and "avoiding eating sweet foods everyday" ($p < 0.05$). These results show that female students have higher fatigue score and lower dietary habits score male students and there was significant relationship between dietary habit and fatigue. Therefore, in order to reduce fatigue, it is necessary to provide nutrition education and counseling for better dietary habit in Korea college students and a further large-scale study is needed about correlation between fatigue and dietary taurine intake.

Dietary nutrients intake including taurine, dietary habit score and dietary quality according to the alcohol consumption level in Korean male college students

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Taurine has a protective property against alcohol-induced damage. To investigate difference of taurine intake according to the alcohol consumption level, we studied anthropometry, intake of dietary nutrients including taurine, dietary habit score and the dietary quality of Korean male college students that were divided according to their alcohol consumption level. Surveys were conducted using questionnaires and a 3 day recall method for assessing dietary intake in 220 male college students residing in Incheon area. The quality of each nutrients intake was assessed using nutrient adequacy ratio (NAR), mean adequacy ratio (MAR), and nutrient density (ND) values. The subjects were divided into two groups by alcohol consumption level: heavy drinking group (average drinking over 5 can (355 ml)s of beer or 7 shot (45 ml)s of soju) and light drinking group (average drinking less than 5 cans of beer or 7 shots of soju or not drinking any alcohol at all at one time during the previous month). The average BMI in the heavy drinking group was significantly higher compared to the light drinking group ($p < 0.05$). There was no significant difference in dietary taurine intake between heavy and light drinking group. The intakes of zinc was significantly lower in the heavy drinking group compared to the light drinking group ($p < 0.05$). The total dietary habit score of heavy drinking group was significantly lower than that of light drinking group ($p < 0.05$). With regard to the diet quality evaluation of subjects, the nutrient densities (ND) of carbohydrate, niacin, vitamin C and zinc in the heavy drinking group were significantly lower than those of the light drinking group. These results show that heavy drinkers have poor dietary habits and low dietary quality. Therefore, continuous nutrition education for heavy drinking Korean male college students may be needed to improve dietary habits and balanced nutritional status and further studies such as case–control study or taurine administration study are required.

Protection by taurine and thiotaurine against biochemical and cellular alterations induced by diabetes in a rat model

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Purpose: To comparatively assess taurine (TAU) and thiotaurine (TTAU) for the ability to attenuate biochemical and cellular alterations associated with diabetes in an animal model.
Methods: Type 2 diabetes was induced in male Sprague–Dawley rats with an intraperitoneal, 60 mg/kg, dose of streptozotocin (STZ) and allowed to progress for 14 days. From day 15 until day 56, the diabetic rats received a single, daily, 2.4 mmol/kg/2 mL dose of either TAU or TTAU in physiological saline by intragastric gavage (treatment groups). Additional diabetic rats were orally treated with a daily 2 mL volume of physiological saline (diabetic group) or subcutaneously with a 4 U/kg dose of isophane insulin (INS) (reference group) from day 15 until the end of the study. Untreated normal rats served as the control group. On day 57, all the rats were sacrificed by decapitation and their blood was collected into heparinized tubes. These samples were then processed for their plasma and red blood cells (RBCs) components. The plasma was analyzed for indices of carbohydrate intolerance, lipid status and oxidative stress, and the red blood cells for evidence of cell membrane integrity, membrane composition, oxidative stress and changes in morphology and in spectrin distribution.
Results: Diabetes led to hyperglycemia, hyperlipidemia, hypoinsulinemia, increased circulating HbA_{1c} level, and to plasma and red blood changes consistent with lipid peroxidation, changes in cellular redox status, and impairment of antioxidant enzyme activities. RBCs showed evidence of hemoglobin leakage, altered membrane cholesterol to phospholipids ratio, spiculated appearance and segregation of the cytoskeletal spectrin towards the periphery. A chronic treatment with INS effectively controlled the hyperglycemia, reversed hypoinsulinemia, attenuated hyperlipidemia, especially hypertriglyceridemia, the increase in HbA_{1c}, and the decrease in the redox status. In addition, it prevented lipid peroxidation and the loss of antioxidant enzymes activities both in the plasma and RBCs; and normalized the morphology of and spectrin distribution in the RBCs. TAU and TTAU were as effective as INS in inhibiting LPO, changes in redox status and oxidative stress in both the plasma and RBC, but much less effective in controlling hyperglycemia and hypoinsulinemia. While INS and TTAU returned the RBCs to their normal biconcave shape and the spectrin to its normal distribution, TAU did not.
Conclusions: Although neither TAU nor TTAU were as potent as INS in preventing diabetes-induced alterations, they were, however, quite protective. In general, while TTAU and TAU offered equivalent protections, differences existed for their effects on the changes in cholesterol to phospholipids ratio, morphology and spectrin distribution, for which TTAU was better than TAU, and on the plasma MDA and triglycerides, for which TAU was better than TTAU.

The effects of taurine and thiotaurine on oxidative stress in the aorta and heart of diabetic rats

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This study was conducted to compare the actions of the sulfur-containing compounds taurine (TAU) and thiotaurine (TTAU) on the oxidative stress that develops in the aorta and heart as a consequence of diabetes. In the study, male Sprague–Dawley rats, 225–250 g, were made diabetic with a single, 60 mg/kg, intraperitoneal dose of streptozotocin in citrate buffer pH 4.5. Starting on day 15 and continuing until day 56, the diabetic rats received a daily 2 mL volume of physiological saline (diabetic group) or 2.4 mmol/kg/2 mL of a sulfur-containing compound (treatment group) in physiological saline by intragastric gavage. An additional diabetic group received a daily 4 U/kg subcutaneous dose of isophane insulin (INS) (reference group). Naive rats served as the control group. The animals were monitored on a weekly basis for body weight gains and blood glucose changes. Following sacrifice of the animals by decapitation on day 57, the hearts and thoracic aorta were immediately collected by the freeze clamp technique, and a suitable aliquot was made into a 1:20 (w/v) homogenate in phosphate buffer pH 7.0 for use in the analysis of parameters of oxidative stress such as malondialdehyde, nitric oxide, reduced glutathione, glutathione disulfide, catalase, glutathione peroxidase and superoxide dismutase. In comparison to control animals, diabetic rats exhibited a decreased growth rate (-34%), higher than normal (by $\sim$4-fold) tail vein blood glucose, marked increase in lipid peroxidation ($\geq$2.8-fold) and catalase activity ($\geq$90%); and decreases in nitric oxide ($\geq$40%), redox status ($\geq$67%) and glutathione peroxidase ($\geq$66%) and superoxide dismutase ($\geq$51%) activities in both the aorta and heart. In contrast, treating the diabetic rats with INS virtually normalized the growth rate and blood glucose level, and, with a few isolated exceptions (aorta catalase, aorta and heart nitric oxide) either abolished or attenuated the changes associated with diabetes to values that did not differ by more than 13% from the control values. Both TAU and TTAU were also significantly protective in the aorta and heart, but, except for changes in the redox status, not as much as INS, particularly in terms of the blood glucose level, lipid peroxidation, and nitric oxide production. While TTAU was generally more protective than TAU, its chronic administration to diabetic rats led to body weight gains than were lower than those of animals receiving either TAU or INS. In summary, the present results strongly suggest that hyperglycemia plays a central role in the development of oxidative stress in diabetes, and that antioxidant compounds such as TAU and TTAU can protect against the losses of enzymatic and nonenzymatic intracellular defenses in both the aorta and heart, more so with the latter than with the former compound, independently of an effect on hyperglycemia.

Rising taurine and ethanol concentrations in nucleus accumbens interact to produce the positive reinforcing effects of alcohol

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Alcohol misuse and addiction is a worldwide problem causing an enormous amount of individual suffering as well as financial costs for the society. We have previously demonstrated that glycine receptors in the nucleus accumbens (nAc) are involved in modulating both basal and ethanol-induced dopamine output in the same brain region. We have also demonstrated that the endogenous glycine receptor ligand taurine mimics ethanol in activating the brain reward system. Ethanol is known to induce a release of both taurine and dopamine in the nAc, but the relationship between these two neuromodulators has not been investigated thoroughly. Here, a series of in vivo microdialysis studies, in freely moving Wistar rats, was used to measure the effects of systemic ethanol diluted in an isotonic (0.9% NaCl) or hypertonic (3.6% NaCl) saline solution with respect to extracellular levels of taurine and dopamine in the nAc. We found that ethanol given in a hypertonic solution, contrary to an isotonic solution, failed to increase concentrations both of taurine and dopamine in the nAc. However, a modest, non-dopamine elevating concentration of taurine in the nAc disclosed a dopamine elevating effect of systemic ethanol also when given in a hypertonic solution. In a second experiment, we investigated the effects of ethanol on taurine and dopamine in normal rats and rats with decreased levels of endogenous taurine. Lowering the level of taurine, approximately 40% by adding 5% beta-alanine in the drinking water, did not influence taurine or dopamine output over time whereas the rate of dopamine elevation were decreased. We conclude that the elevations of taurine and dopamine in the nAc are closely related, and that in order for ethanol to induce dopamine release, a simultaneous increase of extracellular taurine levels in the nAc is required. These data also provide support for the notion that the nAc is the primary target for ethanol in its dopamine-activating effect after systemic administration and that taurine is a prominent participant in activating the brain reward system.

Taurine provides neuroprotection for retinal ganglion cells in different cellular and animal models of glaucoma

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Retinal ganglion cells (RGCs) are neurones, which send visual information to the brain through the optic nerve. RGC degeneration occurs in numerous retinal diseases, either as a primary process like in glaucoma, or secondary to photoreceptor loss in numerous retinopathies. For glaucoma, the second cause of blindness worldwide, current treatments aim at reducing the increase in intra-ocular pressure (IOP) occurred in most glaucoma. Recently, taurine depletion was incriminated in the retinal toxicity of an antiepileptic drug, which leads to the loss of RGCs. Here, we have examined if taurine could directly interfere with RGC survival in different models of RGC degeneration. Thus, taurine effect on RGC survival was firstly assessed in vitro on primary pure RCG cultures from adult rat retinas and in NMDA-treated retinal explants. In vivo, taurine was administered through the drinking water in two glaucomatous animal models with increase in intraocular pressure (IOP) (DBA/2J mice and rats with vein occlusion) and in a model of retinitis pigmentosa with secondary RGC degeneration (P23H rats).

We found that taurine (1mM) incubated into the culture medium for 6DIV, stimulated the survival (+69%) of cultured adult rat RGCs, evaluated by calcein-positive RGC counting. Moreover, addition of taurine (1mM) significantly rescued (+22%) the loss of Brn-3a-positive RGC induced by NMDA excitotoxicity in retinal explants. Long-term oral treatment of taurine (0.2M) in both cauterized rats or in DBA/2J mice did not modify the elevated IOP, but it led to significant recovery of Brn-3a-positive RGC density in DBA/2J mice (+16%) and in rats with episcleral vein occlusion (+87%). In this latter model,

the treatment also prevented the decrease in the photopic ERG. Finally, taurine supplementation also partly prevented the secondary degeneration of RGCs occurring in an animal model of retinitis pigmentosa, the P23H rat.

These data indicated that taurine treatments can stimulate RGC survival in different pathological conditions presenting RGC degeneration. In particular, taurine supplements may therefore provide a new, cheap and simple add-on anti-glaucoma therapy. Future studies are investigating further this new mechanism in which taurine exerts RGC neuroprotection.

Interdisciplinary session

The effect of folic acid on gamma-aminobutyric acid type A ($GABA_A$) receptor beta1 (gabrb1) possible Implication in Autism

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Autism contains a spectrum of behavioral and cognitive disturbances of childhood development that is manifested by deficit in social interaction, impaired communication, and repetitive behavior or restricted interest. It is believe to involved epigenetic of several genes or regulatory region. It has become more evident that autism evolved some sort of defect or deregulation of the gabaergic receptors pathway in the brain. Gamma amino butyric acid type A receptor beta 1 is a subunit involved in inhibitory affects on neurotransmission. The exact mechanism of how $GABA_A$ $\beta 1$ works stills a mystery, but it is evident that it is involved in the pathogenesis of autism,. Folic acid, a vitamin B9, is a methyl donor like many other vitamins B. It is the FDA mandate to increase folic acid intake during pregnancy to anywhere between 800 μg to 5 mg per days, depending on risk levels for spinal bifida. The long-term effect of folic acid rich-diet has no been well investigated. On a recent research, at the New York State Institute of Basic Research by Dr. Junaid and his associates, discovered through DNA microarray analysis that as many 1,000 genes were either up-regulated or down-regulated. One of the genes that it was down-regulated was FmR1, which it has been associated with fragile X disorder. Fragile X overlapped with autism by 37% in phenotype. The FmR1 gene in the knocked mouse has been reported to affect the GABA $\beta 1$ subunit primarily in the forebrain and the cerebellum. The purpose of these series of experiments is to test the effect of different dosages of folic acid on neuronal SY5F cell lines. We performed western blot and qRT-PCR to observe if there is a change in protein expression and quantitative messenger RNA expression is in accordance with dosage of folic acid. Our data indicates an increase in messenger RNA and protein of $GABA_A$ $\beta 1$ receptor protein in the cells that were treated with folic acid. $GABA_A$ receptor subunit $\beta 1$ protein levels increase in the folic acid treated neuronal cells in comparison to control.

$GABA_A$ receptors subunit $\beta 1$ mRNA was up-regulated, and it seem to be folic acid dosage depending in the neuronal cells. The pathway on which folic acid affects the expression of the gene is no known, but it may be implicated in the increase of autism in the recent decades.

Rat GABAergic neural developmental assessment of anxiety, fear potentiation, learning, memory, and pilocarpine induced temporal lobe epilepsy in the rat following chronic low level lead exposure

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Lead (Pb2+) exerts its neurotoxic effects through competition with Ca2+ influx resulting in inhibition of Ca2+-dependent processes and gene regulation. Ca2+ plays a pivotal role in neuronal physiology and Pb2+ exposure during early neural development poses increased risk for the onset of developmental disorders. Children have been identified as the most at risk population for Pb2+ toxicity due to higher degree of gastrointestinal absorption and under developed countries are at greater risk. Once absorbed, Pb2+ is eventually transported and deposited in the brain. Most child phenotypes pose the possibility that Pb2+ may disrupt the maturation of GABAergic neurons during the critical shifts from excitation-to-inhibition balancing which can result in developmental disorders such as: anxiety, attention deficits, learning impairments, memory problems, and potentially autism. We investigated the effects of a chronic low level Pb2+ acetate chow diet (1.5 g/kg) in the Long Evans rat; an established model shown to produce comparable physiological blood Pb2+ levels found in children. Paired male and female rats were exposed to the Pb2+ diet ad libitium and continued throughout development. Age matched offspring at PND 22 age ($N = 14$) were exposed to progressive anxiety producing behavioral assays (open field, elevated plus maze, and context fear test), followed by seizure test ($N = 8$) to identify whether or not Pb2+ disrupts GABAergic maturation. Open fields produced matched levels of anxiety and locomotor activity between treatments. The elevated plus maze revealed increased anxiety in Pb2+ rats by a significant reduction in entries into and time mobile in all zones. The context fear test produced increased freezing responses in Pb2+ rats during learning trials, but reduced retention of the cues with the aversive shock 24 h later. Suggesting that Pb2+ rats exhibit an increased anxiety phenotype that is further enhanced when presented with aversive stimuli that reduce their ability to learn the cues. These observations indicate that the fear potentiated connections between the limbic system and hippocampus may be disrupted as a consequence of Pb2+ toxicity. We investigated the potential GABAergic disruption in the hippocampus through an atropine (1 mg/kg s.c. mAchR antagonist) and pilocarpine (380 mg/kg s.c. mAchR agonist 30 min after) model of epilepsy to test seizure susceptibility. The medial septal-hippocampal pathway is intermingled with ~35–45% cholinergic and ~30% GABAergic neurons. No difference was noted in latency to arrest movement. Contrary to our prediction, control rats exhibited higher rates of progressive seizure stages with quicker onsets, whereas Pb2+ rats were comparably resistant (three fold increased latency to seizures). Our results show that Pb2+ exposure during early development may produce GABAergic disruption in rats when assessed with progressive anxiety tests. Further, this Pb2+-induced anxiety phenotype is enhanced with aversive stimuli negatively effecting learning. When challenged with the pilocarpine seizure test, Pb2+ rats were resistant, suggesting that Pb2+-induced cholinotoxicity of these neurons reducing the excitation of these pathways and failing to evoke seizures. Future studies are needed to investigate the GABAergic seizure susceptibility directly considering the minimal contribution of the cholinergic neurons to evoke seizures under Pb2+ exposure.

IGF-1 role in VEGF-dependent vascular formation of human retinal microvascular endothelial cells

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Retinal vascular formation during development is a complex process that requires temporal and spatial regulations of various factors. Activation of receptor tyrosine kinase (RTKs) by their specific ligands resulted in downstream pathways promoting cell survival, cell proliferation, vascular permeability and cell migration, all lead to angiogenesis. RTK ligands such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) have been shown to be tightly regulated during angiogenesis. In abnormal condition, such as retinopathy of prematurity, it has been shown that there is an abnormal IGF-1 regulation causing the formation of retinal neovascularization. Furthermore, hypoxia-inducible factor (HIF) has been shown to be the transcription factor important in inducing VEGF secretion in certain cells stimulated by hypoxic condition or IGF-1. The goals of this study are to demonstrate in vitro tube formation assay as a model of retinal vascular formation using human retinal microvascular endothelial (HRMVE) cells; and to determine the role of HIF-1a in human retinal angiogenesis affected by VEGF and IGF-1 synergy.

Human retinal microvascular endothelial primary cell lines were grown in chamber slides, once confluent, the cells were treated with VEGF, IGF-1 or both to observe the upregulation of HIF-1a using confocal microscopy. To demonstrate in vitro tube formation assay, HRMVE cell were seeded in growth factor-reduced matrigel medium on 96-well plate with activated media or growth factor-free media in the incubator supplemented with IGF-1, VEGF or both. The cells were intermittently photographed for 24 h in the live imaging chamber. Tube formation assay showed more prominent with the presence of both growth factors, but not on control or in the presence of a single growth factor. In a separate experiment, the HRMVE cells stimulated with IGF-1, VEGF or both were analyzed using Western blot technique to show the upregulation of the HIF-1a. Separately, all experiments above were also done with HRMVE cells pretreated with Wortmannin, a specific phosphoinositide 3-kinase (PI3 K) blocker, to see this particular RTK pathway involvement in retinal angiogenesis. This study demonstrates the crucial roles of IGF-1 through the PI3K pathway in VEGF-dependent angiogenesis in human retinal microvascular endothelial cells.

The influence of hepatocyte growth factor during outer segment phagocytosis by retinal pigment epithelium

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Inhibition of outer segment (OS) processing by retinal pigment epithelium (RPE) has been linked to photoreceptor injury and retinopathy onset; as such, complete understanding of the cellular miscues that precede RPE failure is crucial for maintenance of visual health. Sub-retinal clearance by RPE is facilitated by specialized phagocytosis featuring both RPE specific and traditional FcγR mediated signaling cascades. As a result of this combinatory approach, RPE are capable of internalizing both specific and non-specific external targets alike. The discovery that lack of c-Met signaling results in impairment of phagocytosis in alveolar and hepatocyte macrophages by Huh et al. suggests c-Met's role as modulator of this activity in post-mitotic cells secreting HGF. Since activated PI3K has been identified as an activator of Rac1 during FcγR mediated phagocytosis which is particularly crucial during phagosome closure, we hypothesize that c-Met activation by HGF and subsequent PI3K activation is capable of mediating OS clearance by RPE.

To test our hypotheses, ARPE-19 were cultured with Dulbeccos's Modified Eagle Medium supplemented with 10% fetal bovine serum, 1% pen/strep and 2.5% sodium bicarbonate until they reached 70% confluence and were then serum starved for 24 h. Post starvation, cells were exposed to various concentrations of HGF for 24 h before chemical fixation with 2.5% paraformaldehyde and .5% glutaraldehyde. Employing established immunocytochemical techniques, cells were then prepared for florescence microscopy where receptor expression was evaluated. Intensity values suggest that ARPE-19 respond maximally to concentrations of 25 ng/ml of HGF when compared to controls (0 ng/ml HGF). Similar studies evaluating expression of phosphorylated c-Met, downstream targets of c-Met and binding of non-specific targets were conducted with cells prepared as before. Our findings suggest that RPE respond to increases of exogenous HGF concentrations by up-regulating its receptor and subsequent second messengers systems. In addition, our data show a significant increase of fluorescently labeled *E. coli* and fluorescently labeled latex bead binding. Taken together, these findings suggest that RTK cross-talk initiated by c-Met activation may be sufficient in mediating general uptake of external debris by RPE. Future studies including RPE challenge with fluorescently labeled OS during peak c-Met phosphorylation evoked by increased HGF exposure will provide evidence for HGF's role as a mediator of specialized phagocytosis of OS. Subsequent blockage of c-Met prior to OS challenge and chemical inhibition of PI3K should clarity their roles during this process.

Effect of *Nigella sativa* oil on GABAA-receptor mediated neurobehaviors in mice

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Black cumin oil is the seed extract of *Nigella sativa* Linn that shows promising medical applications. The oil is believed to activate the benzodiazepine site of $GABA_A$ receptor, thus effectively being an agonist for $GABA_A$. Our basis of study is to observe and characterize the effect of black cumin on memory and learning via mouse model. To investigate the effect of black cumin on learning and memory, we delivered black cumin oil into wild-type FVB mice via intraperitoneal injection acutely in 3 mg/kg dosages prior to the start of behavioral testing and analyzed its effect on locomotor activity and task retention. Our preliminary data shows that black cumin treatment results in decreased locomotor activity and deficits in retention of passive avoidance task and Morris water navigation task. These results indicate deficits in learning and memory and may imply $GABA_A$ activation via black cumin. The aim of the proposed research is to examine taurine alternatives as means to studying $GABA_A$ expression in mice. Since *Nigella sativa* is an agonist of $GABA_A$, we suggest that use of black cumin on mice may aid in studying the GABAergic system of Fmr1-KO mice. We hope to extend this research to the

Fmr1-KO mouse model as it has increased seizure susceptibility and hyperarousal parallels symptoms of fragile X syndrome. We expect *Nigella sativa* oil to provide beneficial effects upon learning deficits and epilepsy upon fragile X mouse model. We are currently assessing the anti-epileptic effects of black cumin.

Neurobehavioral effects of prenatal exposure to dibutyl phthalate in juvenile mice

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Dibutyl phthalate (DBP) is man-made phthalic ester that is commonly incorporated into plastic products that frequently come into human contact. Mounting evidence in recent years has shown that DBP is a reproductive toxin that interferes with normal steroid hormone function, with the developing fetus and neonate most susceptible to its effects. In this study, we evaluated the neurobehavioral effects of DBP exposure during early embryonic and postnatal development in both typical mice and in FMR1-KO mice, a widely used animal model of autism spectrum disorder. We have found that offspring of pregnant mice injected with DBP demonstrated sex-specific differences in the open field, elevated plus maze, a passive avoidance task, a 3 day fear conditioning task, and increased susceptibility to kainic-acid induced seizures. These observations suggest that exposure to DBP in pregnant mice appears to result in neurobehavioral abnormalities in their offspring, which may be mediated by alterations in the neuronal circuits associated with these.

Alteration of the photic entrainment of the circadian system in a mouse model of diabetic retinopathy

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Circadian and non-visual responses to light are mediated by a specialized subset of melanopsin expressing retinal ganglion cells as well as rod and cone photoreceptors that provide photic input to mammalian endogenous clock in the suprachiasmatic nucleus (SCN).

Diabetic retinopathy is a major cause of adult blindness and is the most common complication of diabetes since this eye disease affects up to 90% of patients with diabetes. Although vascular damage is considered the first clinical sign of retinopathy, several studies suggest that alterations in retinal neurons and glial cells precede these vascular signs. To explore the hypothesis that this ocular pathology leads to alterations in both the visual and non-visual systems we used a mouse model of diabetic retinopathy. Based on findings that retinal ganglion cells and photoreceptors degenerate during the development of diabetic retinopathy, we address the question to what extent does this impact on the capacity for light entrainment of the circadian timing system.

Diabetes was induced by injection of three successive doses of streptozotocin (SZT), in 3 week-old C57/BL6 wild-type mice, which damages pancreatic β-insulin-producing cells.

Wild type and SZT-induced diabetic male mice were placed under in a light–dark cycle (12L/12D) and subjected to three light intensities (100, 300 and 1,000 lux). Light entrainement was assessed by analysing different parameters such as the total activity during the light and dark phase of the LD cycle under different light intensities and the speed of entrainment (numbers of days necessary to entrain to a new light cycle). Our results showed that under 100 and 300 lux, SZT-induced diabetic mice fail to entrain to the LD cycle whereas control animals entrain at all these light levels. SZT-induced diabetic mice entrain only with increasing levels of light (1,000 lux). In addition, the total activity during the dark phase is similar to the total activity during the light phase in SZT-induced diabetic mice at 100 lux. All these data suggest a decrease in light sensitivity in the SZT-induced diabetic mice. Animals subsequently were subjected to a 6 h phase advance of the LD cycle (1,000 lux), Results show that the SZT-induced diabetic mice require on the average more time (11 ± 0.33 days) to entrain to the new LD cycle than the controls (9 ± 0.23 days).

In conclusion, our results showed that the diabetic retinopathy affect not only visual responses to light but also photic entrainment of the circadian system.

Dopamine modulation of latent inhibition in animal model of Schizophrenia

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Animals with a neonatal ventral hippocampal lesion develop abnormal behaviors during or after adolescence, suggesting that early insults can have delayed consequences. Both the amygdala and hippocampus are implicated in psychiatric disorders as autism, attention-deficit, hyperactivity, and schizophrenia. Disruption of latent inhibition (LI) has been proposed as a possible model of cognitive abnormalities that underlie positive symptoms of schizophrenia.

The present study was undertaken in order to test whether the latent inhibition is disrupted in postnatal lesioned rats using bilateral injection of Lidocaine into the ventral hippocampus.

A neonatal ventral-hippocampal lesion (nVH lesion) was made in 7 days old Sprague–dawley pups. Two groups were formed, the first one received Lidocaine (4 µg/0.3 µl) and the second was constituted by Sham operated control animals. At postnatal day 56, both groups were tested for social contact, locomotor activity in an open field to confirm the establishment of schizophrenia symptoms. The latent inhibition was studied using the conditioned taste aversion paradigm. As LI is known to depend on dopamine transmission during the conditioning phase, it is usually thought that the cognitive processes involved in the establishment of LI during the pre-exposition phase (PE) are dopamine independent. In order to verify the possible involvement of dopamine in the pre-exposition phase, we used a D2 antagonist of dopamine receptors, Haloperidol (0.1 mg/kg) injected before three PE sessions.

The results of histological Nissl stained sections throughout the ventral hippocampus showed that the neonatal bilateral administration of Lidocaine caused some alterations, such as chromatin condensation, nucleolus loss, and cell shrinkage, but without glial proliferation as seen in several studies using Ibotenic acid.

In behavioral study, we reported that the lesion of ventral hippocampus induced several changes that mimic the schizophrenia symptoms. Indeed, at the pubertal age, the animals showed a significant decrease in the number of social interactions and highly increase in the locomotor compared to controls.

Conditioned aversion taste showed that the nVH lesion significantly alters the latent inhibition which was more reduced compared to the control. However, we have shown that the injection of haloperidol, 45 min before each of pre-exposure session in lesioned animals can recover substantially the latent inhibition to values around those of controls.

All behavioral tests and morphological evidences in our study support the idea that the use of Lidocaine as a toxin in the nVH lesion could be a novel model for a neuro developmental hypothesis to study schizophrenia.

Effects of exposure to fenugreek seeds aqueous extract during gestation on locomotor development in mice

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Fenugreek (*Trigonella foenum graecum* (L.)), is a medicinal plant whose seeds are widely used in Moroccan traditional medicine. Consumption of fenugreek seeds during pregnancy has been associated with a range of congenital malformations, including hydrocephalus, anencephaly and spina bifida in human. We previously showed that fenugreek seeds extract (FSAE) had deleterious toxic effects on reproductive performance and potential teratogenic effects in mice fetuses. Behaviorally, pups born from mothers that were treated by fenugreek seeds extract show an alteration in working memory, a hypoactivity and a weaker motor coordination compared with control. These behavioral deficits are associated with a reduction of the brain weight.

The following study was conducted to evaluate the effects of prenatal treatment of fenugreek seeds on the development of motor function. Pregnant mice were treated by gavages with 1,000 mg/kg/day of lyophilized FSAE during the gestational period. Pups were tested for their motor coordination performance during swimming and locomotion. For locomotion; we used the 'CatWalk' automated quantitative gait analysis and the rotarod test. Altered motor coordination in the swimming and the rotarod tests was observed in prenatally exposed mice by FSAE. The stride length, the stance and stepcycle duration, the relative paw position and the cruciate and alternate patterns were affected by FSAE. Then, we investigated whether spontaneous and locomotor-like activities in vitro were altered in prenatally treated mice with FSAE compared with control. Our results showed that the episodes frequency of spontaneous activity was significantly decreased in treated mice (1.238 ± 0.342 compared to 2.886 ± 1.151 for P0–P1 and 0.925 ± 0.512 vs. 1.9 ± 0.627 for P2–P3). Recordings from L2 and L5 ventral roots showed alternating rhythmic discharges in both control and treated mice. The cross-correlation coefficient in control mice was significantly more negative than in treated animals and the period of locomotor like activity was significantly shorter in control mice.

Taken together, FSAE impaired motor and coordination functions in pups but also in adult mice. Moreover, Spinal neuronal networks within are less excitable in prenatally treated mice with FSAE which suggest that it may cause of observed motor impairment in infants.

Effects of nicotine and alkaloids of tobacco plant on extracellular level of dopamine in the striatum and the nucleus accumbens: behavioral correlation

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Nicotine, the main alkaloid fund in tobacco plant, is generally accepted as the chemical responsible for the addictive properties of tobacco. Other alkaloids in the plant have been suggested to participate in the biological action of nicotine. Here, we hypothesized that these molecules modulate the effect of nicotine on the activity of central dopamine (DA) neurons, one of the main cellular target in addiction to drug abuse, as well as on behaviors addressing locomotor activity and anxiety.

Effects of single injection of nicotine and alkaloids of tobacco plant at dose (i.p., 0.5 mg/kg) were investigated behaviorally on locomotor activity in the "open field" (monitored 10 and 35 min post injection), and on anxiety-like status on digging and marble burying test and neurochemically on the efflux of DA monitored in vivo by intracerebral microdialysis in the striatum and the nucleus accumbens of freely moving Sprague–dawley rats. Five to seven days after the stereotaxic implantation of a guide-cannula, a microdialysis probe (2 or 4 mm length, 250 μm) was perfused at a constant flow rate (0.5 μl/min) with an aCSF. Samples (20 min) were analyzed for their DA content by high pressure liquid chromatography coupled to electrochemical detection.

Results show that locomotor activity was significantly enhanced and reduced by nicotine and the extract, respectively, when compared to vehicle-treated rats (number of lines crossed in vehicle-, extract-,nicotine-treated rats: 56 ± 6, 27 ± 3, 106 ± 13). In the digging and marble test, the number of marbles buried in the sawdust in controls (3 ± 0.1) was significantly enhanced in extract-treated (5.8 ± 0.2, $p < 0.01$) only. Neurochemically, nicotine (0.5 mg/kg) enhanced accumbal and striatal DA extracellular levels (+47 and 20% above baseline, respectively). The extract (0.5 mg/kg, ip) evoked also a significant increase in DA extracellular levels in both regions (+33 and +38% above baseline). However, this effect was significantly higher compared to nicotine in the striatum ($p < 0.05$) only.

In conclusion, we provide behavioral and neurochemical evidence that the tobacco extract induces distinct effects compared to sole nicotine as it favors anxiolytic-like behaviors and normalizes the impact of nicotine on the nigrostriatal and mesoaccumbal pathway.

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Effects of prenatal stress by forced swimming on the neurobehavioral development in mice pups

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It is conventionally accepted that prenatal maternal stress affects pregnancy outcome and results in early programming of brain

functions with permanent changes in neuroendocrine regulation and behavior in offspring.

The aim of this study is to compare the effect of tow prenatal stresses by swimming on neurobehavioral change during early postnatal life in mice pups. After confirming their pregnancy, the pregnant mice were divided into three groups: control group, forced swimming (FS) group wish is forced to swim for 10 min once a day from the 10th day of gestation until delivery, and forced swimming against the current (FSAC) group for 5 min once a day, or fewer if the pregnant mouse can't resist to this duration, from the 10th day of gestation until delivery. The mice pups were examined from the 6th postnatal day (PND6), for their motor and vestibular functions using the righting test, and cliff avoidance reflexes.

The cliff avoidance test of pre-stressed offspring's, show a fewer latency (−57.06% in FS group, and −77.88% in FSAC group) for taking away their paws and head from the board compared with control. Furthermore, the righting test shows an improvement of straighten in pre-stressed offspring's. In addition, pups of the FSAC stressed group respond significantly faster than offspring's from FS dams.

Our present study provides the evidence that maternal swimming during the gestational period is not harmful to the offspring development and can represent an exercise that may enhance the brain functions of the mothers' offspring.

Functional recovery after a lesion of the medullar corticospinal tract in Barrelless mice

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The mammalian topographically organized corticospinal tract (CST), arising from layer V neurons in the somatosensory and motor cortex, is the only direct cortical pathway to the spinal cord. Guidance molecules such as Ephrins and Slits are involved at various decision points for guiding the CST axons. The role of the calcium-stimulated adenylate cyclase 1 (AC1) has been revealed in the fine patterning of the retinal maps. Further studies indicated that lack of AC1 disturbed the repulsive response of retinal axon growth cones to ephrin A5.

Because the AC1 gene is highly expressed in layer V cortical neurons during the development of the CST, we questioned whether AC1 is involved in the targeting of the CST and in regeneration after a lesion. We used the barrelless (brl) mouse strain which carry a spontaneous mutation of the AC1 gene and investigated the projections of the CST in the cervical spinal cord using anterograde tracers. We also analysed corticospinal neurons in the motor cortex using retrograde tracers. To investigate the effects of AC1 on axon regeneration in vivo, the brl mice were tested in a model of spinal cord injury (SCI) by a dorsal hemisection at T8–T10.

Our study shows an increase in the number of contralateral and ipsilateral projections in the cervical spinal cord in brl mice in comparison to controls. Moreover, the density of labeled neurons in the motor cortex is significantly higher in the brl mice. However no major abnormalities of the CST were detected. Concerning the functional recovery after spinal injury, results indicate that it was more greater and earlier in brl mice than in control.

The targeting defects observed in our study could be linked to activity dependent remodeling of the CST, and maintenance of exuberant axonal branches in absence of AC1 as have already demonstrated for by our team for the visual system. The increase in the number of corticospinal axon terminals in the main tract may explain the enhanced functional recovery after a spinal cord injury.

Thinner exposure affects spatial memory in C57 mice

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Cognitive dysfunction due to chronic organic solvent exposure has been found in a number of clinical and epidemiological studies of human subjects including solvent-exposed workers and solvent abusers.

In this study we investigated the effect of a single and chronic exposure on cognitive function especially spatial memory using Morris Water Maze task. Four groups of C57 mice (N = 5, each) were used; a control group and tree group exposed to inhalation of the thinner (0.2, 0.3, 0.4 ml) in a static chamber for 4 months (1 h/day). The test was started at the end of last day of exposition.

Our results showed that an acute inhalation have no significant effect on memory abilities. These results indicate that mice exposed chronically to thinner have a significantly increased latency to find the hidden platform and cover a significant longer distance (Path length), compared to control in the learning phase of the Morris Water Maze. The chronic exposure alters both learning and spatial memory. This effect was dose dependent since the group receiving 0.2 ml didn't showed any impairment in cognitive abilities, while the groups receiving 0.3 and 0.4 ml, had difficulties to find the hidden platform.

In conclusion, the present findings indicate that chronic inhalation exposure to thinner influences spatial learning memory, and the effect was dose-related concentration and/or duration of exposure.

Role of voltage sensitive calcium channels (VSCCs) in the maturation of the GABAergic system in the Fragile X syndrome

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GABAergic system, particularly the $GABA_A$ receptor-mediated function, has been reported to be altered in fragile X syndrome. $GABA_A$ receptor is considered to be a major inhibitory receptor in the brain. A significant down-regulation of the $GABA_A$ receptor in the *Fmr*1 KO mice has been demonstrated in recent researches, which may underlying the mechanism for the anxiety, hyperactivity found in fragile X syndrome patients. However, during development, activation of $GABA_A$ receptor exerts both inhibitory and excitatory effects on the neuronal network. The excitatory effect of $GABA_A$ receptor early on set the major tune in generating giant depolarizing potentials (GDPs), recurrent synchronized spontaneous network discharges which is a feature of neuronal activity of developing neurons. GDPs control extension and motility of neuritis as well as synthesis and expression of the GABAergic phenotype through the activation of voltage sensitive calcium channels during early developmental up to P14. The developmental shift in the $GABA_A$ receptor function from excitation to inhibition is dependent upon the expression level of both

cotransporters NKCC1 and KCC2, of which KCC2 is a major regulator. We examined the expression level of KCC2 during early developmental stages of mice at P1, P3, P5, P7 and P10 in both wild type (WT) and *Fmr*1 KO mice (KO) groups. A markedly increased expression of KCC2 was detected in both groups, which indicates the occurrence of functional shift of the $GABA_A$ receptor. Interestingly, a shift in the peak KCC2 expression in the KO group was found. It is suggested that the depolarizing effect of the $GABA_A$ receptor during KO brain development is disrupted. KCC2 expression is calcium mediated. Thus, we hypothesize that pharmacological manipulation to KO mice with voltage sensitive calcium channel (VSCC) activator at embryonic stages may help to correct the malfunction of the GABAergic system.

The characterization of Pb^{2+} toxicity in the rat cardiovascular system: an assessment of Pb^{2+} induced pathophysiology

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In this study, we investigated the relationship between blood pressure and chronic lead exposure in Long Evans rats in various ages. Furthermore, we examined histologically the collagen and elastin fibers from rats treated chronically with lead. Using a scanning electron microscope to examine the ultrastructure of the tunica interna and externa, we found that the collagen and elastin fibers were drastically reduced in thickness. Furthermore, the waviness of these layers was reduced, indicating a reduced elasticity of the wall of these vessels. Consistent with this, we found that rats treated chronically with lead had sustained hypertension compared to age matched controls. Concomitant with chronic hypertension, these had an elevated heart rate due to the increased resistance of blood vessels. This in turn resulted in a significant increase in the thickness of the myocardium. Therefore, functional, anatomical and histological indicate that lead toxicity on the cardiovascular system is mediated through an increase in heart rate, blood pressure and thickness of the myocardium.

Prenatal stress in rats influences the vaginocervical sensitivity: study of c-fos expression in the spinal cord of the offspring

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Previous studies in humans have reported a link between maternal stress and disturbed infant physiological behaviour. The prenatal stress is considered as an early epigenetic factor able to induce long lasting alterations in brain structures and functions, inducing long term behavioural abnormalities and changes in the hypothalamo-pituitary-adrenal axis. It enhances also the secretion of adrenocorticotropin releasing hormone (ACTH) and corticosterone, and increased activation of the sympathetic nervous system.

The objective of our study was to examine how maternal prenatal stress induced by a forced swim in experimental rats affects offspring afferent spinal responses mediated by stimulation of vaginocervical receptors. The activation of spinal cord neurons materialized by c-fos expression was examined following vaginocervical mechanical stimulation in adult female offspring of dams exposed to gestational stress from E10 until delivery. Vaginocervical stimulation of both prenatal-stressed and non-prenatal-stressed rats induced an increase in expression of Fos protein in the spinal cord from T12 to S1 levels. However, a significantly higher (40%) increase of Fos-immunoreactive neurons was observed in vaginocervical stimulated prenatally stressed rats than in non-stimulated prenatally stressed ones. This increase was higher in L5–S1 levels than in T12–L4. When the regional distribution was examined, results showed that up to 80% of activated neurons were located in the dorsal horn in both non-stimulated prenatally stressed and stimulated prenatally stressed groups, with a significantly higher density in the latter. Our results demonstrate that maternal prenatal stress can have consequences on vaginocervical responses conveyed to the spinal cord. The increase in Fos labeled neurons in T12–S1 in prenatally stressed rats induced by vaginocervical stimulation suggests the hypersensitivity of the genital tract associated with activation of spinal circuits spanning multiple segments.