Amino Acids (1991) 1: 289–292

Amino
Acids

Biological activity of alpha-alkyl-amino acids

Short communication

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Summary. A series of alpha-alkyl-amino acids were tested for some biological functions in the mouse (OF-1 Himberg) by adding them to the animal chow (30 mg/kg/day) for a period of six weeks. No differences in fluid or food uptake could be observed during the feeding period, as compared to a control group. Histology of liver and kidney did not show any changes. Testing routine clinical chemical parameters (serum substrates and enzymes) revealed the following changes: Hex-Ala and But-Abu increased the serum glucose levels. But-Abu dramatically lowered the triglycerides. Serum albumin was increased by Pent-Ala, Me-Val, and But-Abu. LDH was inhibited by But-Abu.

Keywords: Amino acids – Alpha-alkyl-amino acid biology – Reaction on triglycerided, -albumin, -glucose – Lipid metabolism

Introduction

Alpha-alkyl-amino acids are also known as 2-alkyl-AA, alpha-alpha-dialkyl-alpha-amino acids or C alpha-alpha dialkylglycines.

They are present in naturally occurring and synthetic polypeptides [1]. Examples are the presence in mycotoxins [2] or in the antibiotic amicetin [3]. They are in use for peptide modelling and as tools for drug design [4]. Another application of alpha-alkyl amino acids (AAAA) is the use for metabolic studies: they are known not to be metabolized [5]. The knowledge on biological functions is very poor. In order to find a biological role we tested a series of AAAA in the mouse system.

Table 1

	controls	But-Ala	Pent-Ala	Hex-Ala	Hept-Ala	Oct-Ala	Non-Ala	Me-Val	But-Abu	Pent-Abu	Hex-Abu
CK U/l	133.3 ± 41.7	119.8 ± 71.5	105.9 ± 32.5	96.3 ± 51.0	107.7 ± 29.8	106.8 ± 66.5	112.3 ± 38.7	203.3 ± 152.9	152.3 ± 70.7	158.8 ± 68.4	181.6 ± 82.1
LDH U/l	464.4 ± 73.8	504.2 ± 151.6	502.6 ± 202.9	441.4 ± 177.1	389.5 ± 93.9	458.8 ± 145.5	392.4 ± 119.3	461.8 ± 186.4	339.1 ± 75.3	466.0 ± 184.5*	462.1 ± 80.1
BUN mg/dl	18.4 ± 4.1	18.4 ± 5.5	20.0 ± 3.9	22.7 ± 8.6	22.2 ± 5.6	18.5 ± 5.3	18.5 ± 6.8	25.6 ± 14.7	19.7 ± 7.6	19.0 ± 7.3	20.0 ± 9.1
GPT U/l	37.7 ± 4.9	44.2 ± 8.9	41.0 ± 3.2	40.3 ± 6.0	34.7 ± 3.7	42.3 ± 7.9	39.3 ± 3.3	40.3 ± 4.6	38.4 ± 3.2	38.3 ± 2.6	41.3 ± 5.8
Alb mg/10 ml	151.4 ± 20.3	162.4 ± 16.2	168.9 ± 12.9	166.6 ± 19.9	148.4 ± 17.3	155.1 ± 10.8	143.0 ± 28.4	191.9 ± 31.2	179.3 ± 21.8	170.6 ± 14.9	174.9 ± 27.7
Gluc mg/dl	123 ± 13	111 ± 20	125 ± 16	146 ± 14	126 ± 13	124 ± 19	126 ± 26	140 ± 21	143 ± 18	138 ± 21	145 ± 22
GOT U/l	57 ± 12	63 ± 17	65 ± 10	58 ± 1.0	48 ± 8	58 ± 13	54 + 10	53 ± 13	47 ± 11	49 ± 16	50 ± 13
A.P. U/l	140 ± 48	140 ± 24	151 ± 23	165 ± 47	137 ± 35	149 ± 55	136 ± 47	153 ± 59	159 ± 39	146 ± 22	158 ± 31
Prot. mg/10 ml	446 ± 61	472 ± 28	489 ± 24	484 ± 27	455 ± 29	466 ± 15	446 ± 55	498 ± 40	480 ± 34	469 ± 23	481 ± 40
TG mg/dl	115 ± 47	141 ± 57	154 ± 6.0	124 ± 51	103 ± 39	122 ± 36	128 ± 41	83 ± 34	67 ± 20	63 ± 21	76 ± 26

Material and methods

140 mice (OF-1 Himberg), female, white, 6 weeks of age, were used. They were divided into 14 groups to ten mice each. 13 groups received AAAA preparations and 1 group served as control.

The AAAA were added to the animal chow (Altromin 1321ff). The dosage of administered AAAA was 30 mg/kg body weight/day. The fluid and food intake and body weight was recorded weekly. After a period of six weeks animals were sacrificed by diethylether treatment. Blood was drawn and spun down to obtain sera. Sera were kept until examination at −30 centigrades.

Organs were taken at autopsy and kept frozen. Liver and kidney biopsies were taken for histology.

The following serum parameters were estimated on a Greiner G400 autoanalyzer: sodium, potassium, calcium, chloride, phosphate, cholesterol, triglycerides, glucose, blood urea nitrogen, creatinine, uric acid, bilirubin, total protein, albumin, gamma GT, GOT, GPT, LDH, alkaline phosphatase, amylase, creatine kinase.

Results

The animals did not differ in fluid and food uptake or in body weight.

Histological examinations of liver and kidney did not show any pathological changes.

Values not given in table 1 did not show any statistical differences or abnormalities in comparison to the control panel.

Discussion

The most prominent biological findings were the influences on glucose, triglycerides and albumin metabolism. Butyl-amino butyric acid and hexyl-aminobutyric acid but not its analogue pentyl-amino butyric acid increased serum glucose levels. The mechanism of action remains unclear. As body weights, food and fluid intake in the groups with elevated serum glucose levels were statistically comparable, nutritional factors e.g. Mast, endocrine pancreatic function i.e. relative or absolute insulin deficiency, cannot be incriminated. Gluconeogenetic effects are the most probable hypothetic mechanism. The cited compounds are considered as counterparts of the hypoglycemia inducing amino acid hypoglycin which occurs in plants.

The second phenomenon, the decrease of serum triglycerides, cannot be mechanistically explained as well. Butyl-amino butyric acid as well as pentyl amino butyric acid showed the triglyceride lowering effect but this was not the case for hexyl-amino butyric acid. Structural analogy to nicotinic acid, known to reduce serum triglycerides does not exist. In contrast, clofibrate shows some analogy to butyl- and pentyl-amino butyric acid. Clofibrate is chlorophenoxy-isobutyric acid ester.

If the structural relationship to the clofibrate group is accepted, a related action mechanism of hepatic lipoprotein release inhibition could be incriminated. Bezofibrate and fenofibrate as clofibrate analogues are known to inhibit triglyceride synthesis, bezafibrate also increases LDL degradation, leading to reduced serum triglyceride levels.

The third main observation, the increase of serum albumin might be explained by increasing the resistance against proteolytic cleavage, a mechanism described for exo and endoproteases [6]. This mechanism could be responsible only in the case that AAAA are incorporated into proteins. This was not tested. For the related compound alpha-amino isobutyric acid, however, it is shown that it is not being incorporated into proteins. An alternative mechanism of action could be the inhibition of proteolytic enzymes directly. We have no evidence yet for the inhibition of proteases but butyl aminobutyric acid inhibited in our experiment an enzyme: serum lactate dehydrogenase.

Our first results are preliminary observations but with promising pharmacological aspects. The absent toxicity of AAAA along with the state of being non metabolized makes AAAA a promising field for the development of anabolic and antilipemic drugs.

References

1. Payne JW, Jakes R, Hartley BS (1970) Biochem J 117: 757
2. Brückner H, König W, Aydin M, Jung G (1985) BBA 827: 51
3. Flynn EH, Hinman JW, Caron EL, Woolf DO (1953) J Am Chem Soc 75: 5867
4. Mutter M (1985) Angew Chemie 97: 639
5. Noall MW, Riggs TR, Walker LM, Christensen HN (1957) Science 126: 1002
6. Turk J, Marshall GR (1975) Biochemistry 14: 2631

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Verleger: Springer-Verlag KG, Sachsenplatz 4–6, A-1201 Wien. – Herausgeber: Prof. Dr. Gert Lubec, Muscle and Collagen Research Group, University of Bristol, Langford, Bristol BS18 7DY, U.K. – Redaktion: Sachsenplatz 4–6, A-1201 Wien. – Satz und Umbruch: Asco Trade Typesetting Limited, Hong Kong; Reproduktion und Offsetdruck: Novographic, Ing. W. Schmid, Maurer-Lange-Gasse 64, A-1238 Wien. – Verlagsort: Wien. – Herstellungsort: Wien. – Printed in Austria.