Drugs of the Future 2010, 35(2): 155-159

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.2.1468917

MEETING REPORT

NEW THERAPEUTIC APPROACHES IN EPILEPSY AND COMORBID DISORDERS

HIGHLIGHTS OF THE 63RD ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY

A. Dhir

Department of Neurology, University of California Davis Medical Center, Sacramento, California, USA

CONTENTS

SUMMARY

The 63rd Annual Meeting of the American Epilepsy Society was held in Boston, Massachusetts, USA on December 4-8, 2009. The meeting was attended by more than 4,000 delegates involved in both basic and clinical aspects of epilepsy across the globe. The topics of deliberation were divided into symposia, special lectures and poster presentations. Epilepsy is one of the world's oldest known neurological conditions and is associated with a high degree of social stigma and discrimination. According to a report from the World Health Organization (WHO), approximately 50 million people worldwide suffer from epilepsy. Unfortunately, patients suffering from epilepsy have a greater probability of developing other comorbid neurological complications, such as major depression, anxiety and dementia. Despite the availability of more than 25 antiepileptic drugs, approximately 30-40% of the epileptic population does not attain complete remission. Various novel drug targets and therapies have been identified to treat epilepsy. These new drugs are expected to have a better safety profile compared to currently available drugs. However, we still need to investigate many unanswered questions in epilepsy and emphasis should be placed on the development of target-specific novel drug therapies. Therefore, organizing such meetings and presenting new outcomes in the field of epilepsy may unlock new treatment options for these patients. The present review attempts to synthesize outcomes of the deliberations in the field of epilepsy that were discussed at the meeting.

Correspondence: Ashish Dhir, M.Pharm, PhD, Department of Neurology, University of California Davis Medical Center, 4635 2nd Ave. - Research I, Suite 1004A, Sacramento, CA 95817, USA. E-mail: ashishdhirpu@yahoo.com.

INTRODUCTION

The American Epilepsy Society is one of 98 chapters of the International League Against Epilepsy (ILAE) and is considered the oldest neurological society in the U.S. The society is the premier organization of clinicians and basic scientists that aims to support research and education dedicated to the prevention, treatment and cure of epilepsy. The 63rd Annual Meeting of the American Epilepsy Society was held in Boston, Massachusetts, USA, on December 4-8, 2009. Boston is an education hub of America with world-class educational institutions. The meeting was attended by more than 4,000 epilepsy care professionals from all over the globe, including neurologists, neurophysiologists, epileptologists, neuroscientists, neurosurgeons, internists, pediatricians, pharmacists, nurses, social workers and other epilepsy care professionals. The meeting discussed some of the novel outcomes in the area of epilepsy research, which include the discovery of novel antiepileptic drugs such as eslicarbazepine acetate and brivaracetam, mTOR (mammalian target of rapamycin) inhibitors, clinical trials with antiepileptic drugs, pediatric epilepsy care, the association of comorbid disorders such as anxiety and major depression, the future of epilepsy therapy, surgical options available for epileptic patients and the intrapulmonary approach of antiepileptic drug administration. Different pharmaceutical companies involved in exploring novel targets in the field of epilepsy also presented their preclinical and clinical experiences with these molecules.

Epilepsy is a chronic neurological disorder characterized by recurrent seizures caused by sudden, usually brief, excessive electrical dis-

charges in a group of brain cells (neurons). Approximately 70% of cases of epilepsy are idiopathic/cryptogenic with no underlying cause. In contrast, 30% of epileptic patients have identifiable diseases or brain abnormalities, such as brain tumors, infections, fever (febrile seizures), head trauma, stroke, inborn errors of metabolism, etc. An imbalance between excitatory and inhibitory neurotransmitter systems in the brain can lead to many neurological disorders, including epilepsy. For example, according to the classic theory explaining the pathophysiology of epilepsy, there is an excessive release of glutamate (excitatory neurotransmitter) or a decrease in γ-aminobutyric acid (GABA; inhibitory neurotransmitter). In addition to glutamate and GABA, adenosine is equally important in seizure activity and disturbances in the adenosinergic system may also lead to the onset of seizures. Also, there is excessive sodium and calcium channel-induced neuronal depolarization leading to excessive firing of neurons and thus "hyperexcitable neurons". Therefore, the approach employed to treat epileptic patients is to either block the excitatory pathway or enhance the inhibitory neurotransmitter pathway in the brain.

Based on this concept, more than 25 antiepileptic drugs are available on the market. These drugs were mainly discovered through serendipity. Unfortunately, despite the availability of these antiepileptic drugs, approximately one-third of the epileptic population still continues to have seizures. Therefore, it is very important to discover novel antiepileptic drugs based on our understanding of cellular and molecular mechanisms in epilepsy. These novel drugs are expected to possess better efficacy and safety profiles compared to currently available agents. By discovering new drugs based on novel targets, we hope to treat the remaining 30-40% of the epileptic population that does not respond to current antiepileptic drugs. The present review discusses some of the deliberations held at the 63rd Annual Meeting of the American Epilepsy Society.

ESLICARBAZEPINE ACETATE: A NEW ANTIEPILEPTIC MOLECULE

Eslicarbazepine acetate is a new once-daily antiepileptic drug that proved effective in clinical trials for the treatment of partial-onset seizures. The structure of eslicarbazepine resembles that of carbamazepine and oxcarbazepine in that it possesses a dibenzazepine nucleus ring bearing a 5-carboxamide substituent. However, it differs structurally from carbamazepine and oxcarbazepine at the 10,11-position. This prevents the formation of toxic epoxide during the metabolism of eslicarbazepine (1). This novel molecule acts by inhibiting voltage-gated sodium channels, thereby reducing the hyperexcitability of neurons. In a multicenter, double-blind, randomized, placebo-controlled study including 143 patients (18-65 years of age) with at least 4 partial-onset seizures per month, it was found that eslicarbazepine acetate at a dose of 800 mg once daily reduced seizure frequency compared to the placebo control group. During the phase III studies of eslicarbazepine in subjects with partial-onset epilepsy, a dose of 800 mg did not have any pharmacokinetic interactions with carbamazepine, levetiracetam, lamotrigine, topiramate and valproate (2). Eslicarbazepine acetate was well tolerated and resulted in continued decreases in seizure frequency over the 1-year treatment period (3). The molecule has been found to improve quality of life with once-daily dosing in adult patients with epilepsy suffering from partial-onset seizures (4).

mTOR INHIBITORS IN EPILEPSY

mTOR, or mammalian target of rapamycin, is a serine/threonine-protein kinase involved in protein synthesis related to cell growth and proliferation, angiogenesis and cell metabolism, and also regulates neuronal development and synaptic plasticity (5, 6). The mTOR pathway is dysregulated in many disorders, such as diabetes, obesity, cardiovascular disease, cancer and neurological diseases. Rapamycin is an immunosuppressive agent that acts by directly binding to mTOR complex 1 (mTORC1) and has been approved for the prophylaxis of organ rejection in patients aged 13 years or older who receive renal transplants. Several other disorders, including tuberous sclerosis complex (TSC; a genetic disorder that causes tumors to form in many different organs, including the brain), focal cortical dysplasia (a wide range of alterations of the cortical mantle), hemimegalencephaly (a rare disorder in which one side of the brain is bigger than the other) and ganglioglioma (a tumor that arises from ganglion cells in the central nervous system) are also associated with an altered mTOR signaling pathway. Most of these disorders are highly associated with a risk of developing epilepsy. Therefore, it can be speculated that inhibiting mTOR using rapamycin can be a useful therapy in epilepsy associated with the above-mentioned disorders.

In one of the symposia held at the American Epilepsy Society meeting, the usefulness of rapamycin in epilepsy was discussed (7). Rapamycin has demonstrated potential in treating epilepsy associated with tuberous sclerosis. Tuberous sclerosis is a genetic disorder associated with mutations in either TSC1 (tuberous sclerosis 1 protein) or TSC2 (tuberous sclerosis 2 protein) and can lead to epilepsy, mental retardation and autism (8). The neuronal TSC1 knockout mouse is available and known to exhibit hyperactivity, tremor, seizures, poor weight gain and a median survival of 33 days (9). Several preclinical studies have depicted the role of mTOR in the pathophysiology of epilepsy. In one study, the mTOR pathway was shown to be activated following kainic acid-induced status epilepticus, and rapamycin pretreatment decreased seizure-induced cell death and spontaneous seizures. Also, treatment with rapamycin after status epilepticus blocked late mTOR activation and spontaneous seizures (10). Based on these studies, it can be speculated that rapamycin may be a useful therapy for patients with epilepsy associated with tuberous sclerosis.

INTRAPULMONARY APPROACH TO DELIVER ANTIEPILEPTIC DRUGS

Another interesting lecture given at the meeting addressed the intrapulmonary approach to deliver antiepileptic drugs. The intrapulmonary route is considered to be the fastest route of drug action and has been attempted for many molecules, including antiasthmatic, antidiabetic and, more recently, antimigraine agents. This route can potentially be useful for delivering antiepileptic drugs into the brain. The lungs are highly vascularized tissues that receive their blood supply directly from the right side of the heart via the pulmonary arteries. Inhaled agents are rapidly absorbed into the bloodstream and bypass first-pass metabolism in the liver. The blood exiting the lungs is directly carried to the brain via the carotid arteries. The inhaler device is expected to be used by patients experiencing an aura or warning of an impending seizure by a seizure prediction

device to abort the onset of a full-blown seizure. Researchers have carried out preclinical experiments using propofol hemisuccinate, an aqueous prodrug of propofol, in animal models of seizures. Propofol was chosen because it is a powerful anticonvulsant that is employed to abort status epilepticus. Moreover, it has a quick onset of action and a fast clearance rate. Therefore, when inhaled, only minute quantities (μg) may be sufficient to abort the onset of full-blown seizures, and the patient can resume daily activities after a few minutes of sedation caused by propofol. Such an inhaler system is considered to be the future for the management of acute attacks of epilepsy in patients suffering from temporal lobe epilepsy with aura, and also status epilepticus (11, 12). However, this approach requires clinical testing.

COMORBID NEUROLOGICAL DISORDERS IN EPILEPSY

Like other chronic illnesses, epilepsy affects the patient's quality of life and interferes with daily activities. Depression is a common comorbid disorder associated with epilepsy. Many theories have been proposed to explain the occurrence of depressive symptoms in patients suffering from epilepsy, including: 1) an altered metabolic state of neurons; 2) a psychological component of epilepsy; 3) the adverse effects of some antiepileptic drugs; and 4) serotonin disturbance as a common pathophysiological factor in both depression and epilepsy (13). Chronic administration of antiepileptic drugs has also been associated with mood fluctuations. Drugs such as barbiturates, vigabatrin and topiramate pose a greater risk, while tiagabine, levetiracetam and felbamate are associated with an intermediate risk for depressive disorders in epilepsy (14, 15). In contrast, antiepileptic drugs such as phenytoin, ethosuximide, carbamazepine, oxcarbazepine, gabapentin, sodium valproate, pregabalin and lamotrigine are associated with a low risk for depression, and some may even alleviate the mood disorder (14). For example, in one clinical study, lamotrigine was found to improve the symptoms of depression in patients suffering from epilepsy (16). In another study, post-status epilepticus rats demonstrated an increase in immobility in the forced swim test, demonstrating a depression-like state. Furthermore, the effect was reversed by chronic administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (17). Interleukin-1β (IL-1β) has also been found to be involved in the pathophysiology of both temporal lobe epilepsy and clinical depression. Infusion of recombinant IL-1 receptor antagonist (IL-1ra) to the hippocampus of post-status epilepticus rats improved depressive symptoms such as anhedonia and despair, dysregulation of the hypothalamo–pituitary–adrenocortical axis and compromised raphe–hippocampal serotonergic transmission (18).

In one presentation at the meeting, the bidirectional comorbidity between epilepsy and psychiatric disorders was discussed. Patients suffering from epilepsy, in particular temporal lobe epilepsy, have a higher risk of developing depression and patients with a history of depressive disorder or suicide attempts are more likely to develop epilepsy (19). Other neurological disorders, such as anxiety, attention deficit, psychotic and personality disorders, are also associated with epilepsy. Often, seizure remains the focus of clinical care in patients suffering from epilepsy, although behavioral disorders may also be troublesome for the patient and the family. Antidepressant drugs such as SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) are considered to be safe for treating patients suffering from comorbid depression and epilepsy (20).

In another talk at the meeting, the role of serotonin in the pathophysiology of both epilepsy and depression was discussed (21). The 5-HT_{1A} receptor is involved in the pathophysiology of both major depression and epilepsy. A decrease in 5-HT_{1A} receptor binding has been demonstrated in various regions of the brain, such as amygdala, hippocampus, temporal cortex, insula, anterior cingulate and the raphe nucleus, ipsilateral to seizure origin of patients suffering from temporal lobe epilepsy (19, 22). These regions of the brain are involved in the pathogenesis of both epilepsy and major depression.

Epilepsy and dementia are also linked with each other (23). In a prospective cohort study, it was concluded that unprovoked seizures occur more frequently in patients suffering from Alzheimer's disease compared to the general population (24). Another study has shown that seizure incidence is increased in subjects with mild to moderate Alzheimer's disease (25). It has been demonstrated that fibrillar β-amyloid (Aβ) is responsible for altering neuronal membranes, producing hyperexcitability of pyramidal cells, which culminates in epileptiform activity (26).

NEUROINFLAMMATION AND NEUROEXCITABILITY

Neuroinflammation plays a role in almost all neurological disorders. Various findings have suggested that targeting inflammatory processes in the brain can be protective in treating schizophrenia, depression, Parkinson's disease and Alzheimer's disease. At the meeting, the involvement of neuroinflammation in epilepsy was a topic of debate (27).

Cytokines are known to be involved in the pathophysiology of epilepsy (28). In one study, focal application of kainic acid in the rat hippocampus resulted in enhanced IL-1β immunoreactivity in glial cells. Moreover, injection of IL-1β shortly before kainic acid enhanced seizure activity; the effect was blocked by selective antagonists of IL-1β and *N*-methyl-D-aspartate (NMDA) (29). This suggests that IL-1β worsened the seizure activity by modulating glutamatergic neurotransmission. This was further confirmed by Viviani et al., who demonstrated that IL-1β enhanced the NMDA receptor-mediated intracellular calcium increase through activation of tyrosine kinases and subsequent NR2A/B subunit phosphorylation (30). Moreover, proinflammatory cytokines can prevent astrocytic glutamate uptake, resulting in elevated extracellular glutamate levels and hyperexcitability (31). IL-1β is known to aggravate epileptic activity, contribute to neurodegeneration and increase blood–brain barrier permeability. In another study presented at the meeting, it was shown that rats with traumatic brain injury demonstrate microglia and astrocyte activation, which leads to more IL-1β production. Enhanced IL-1β production can be damaging to neurons and may be considered one of the possible causative factors for brain injury-induced epilepsy (27).

In addition to the involvement of cytokines in the pathophysiology of epilepsy, various animal studies have demonstrated the protective effect of cyclooxygenase (COX) inhibitors in epilepsy. COX is a key enzyme involved in the synthesis of prostaglandins and leukotrienes and exists in two isoforms, COX-1 and COX-2. COX-1 is the constitutively expressed isoform, while COX-2 is the inducible isoform. Various studies have demonstrated the protective effect of COX-2

inhibitors in animal models of epilepsy. The mechanism is not yet clear, but is hypothesized to be mediated through modulation of GABAergic neurotransmission (32). Therefore, we hope that targeting neuroinflammation may be a future line of treatment for patients suffering from pharmacoresistant epilepsy.

KETOGENIC DIET AND EPILEPSY

The ketogenic diet has been considered since the 1920s to control intractable seizures. The diet comprises high fat, adequate protein and low carbohydrate contents (33), and is considered to reduce seizure frequency and to be suitable for children who continue to have seizures despite treatment with antiepileptic drugs (34). In one study reported by Ginzberg et al., approximately 10 pharmacoresistant patients (8 months to 19 years of age) were treated with the ketogenic diet. These cases were not responding to any antiepileptic drugs (35). In a recent randomized clinical trial involving 145 patients, the ketogenic diet was proven effective in children with intractable epilepsy (36). The ketogenic diet is a promising therapy for patients with myoclonic–astatic epilepsy, a malignant epilepsy syndrome that often proves refractory to antiepileptic drug treatment (37). The mechanism of the protective effect of the ketogenic diet is not completely understood, but it is hypothesized to entail: 1) alteration of the levels of GABA and other cerebrospinal fluid amino acids; 2) change in mitochondrial biogenesis; 3) anticonvulsant properties of ketone compounds such as acetone; 4) neuroprotective mechanisms via shielding from free oxygen radicals by inducing glutathione peroxidase; and 5) prevention of apoptosis by increasing the levels of the protective protein calbindin (33). In a study discussed at the meeting, the long-term health and seizure outcomes of children treated with the ketogenic diet were studied. It was concluded that the ketogenic diet has long-lasting beneficial effects in controlling seizures but does not affect growth, lipids, liver or kidney functions in patients (38). In another study presented at the meeting, the ketogenic diet was found not to produce dyslipidemia when tested in 12 children with intractable epilepsy. These children were started with the ketogenic diet and fed a high-fat formula at a 4:1 ratio. There was a significant decrease in low-density lipoprotein (LDL) levels after 12 months of the ketogenic diet, while the levels of cholesterol, triglycerides and high-density lipoproteins (HDL) were not affected (39).

CONCLUSIONS

The American Epilepsy Society continues to be an exciting platform for the presentation and propagation of cutting-edge epilepsy-related basic and clinical data. Maintaining its traditions, the 63rd Annual Meeting of the American Epilepsy Society discussed novel outcomes in the field of both basic and clinical research in epilepsy. Various comorbid neurological disorders, such as major depression, anxiety and dementia, are often associated with epilepsy. Treatment of these disorders is as important as treating seizures in these patients. Based on our understanding of the pathophysiology of epilepsy and the ongoing research exploring novel targets, we hope to be able to treat the remaining 30-40% of the epileptic population that is still not seizure-free.

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Almeida, L., Soares-da-Silva, P. *Eslicarbazepine acetate (BIA 2-093).* Neurotherapeutics 2007, 4(1): 88-96.
2. Bialer, M., Falcão, A., Maia, J., Almeida, L., Soares-da-Silva, P. *Investigation of the influence of eslicarbazepine acetate on the plasma concentrations of concomitant antiepileptic drugs in patients with partial onset epilepsy.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Scientific Exhibition.
3. Trinka, E., Halász, P., Elger, C. et al. *Term treatment of partial onset seizures with eslicarbazepine acetate (ESL): Results of a one-year open-label extension to study BIA-2093-301.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Scientific Exhibition.
4. Cramer, J., Elger, C., Halász, P. et al. *Assessment of quality-of-life and depressive symptoms during long-term treatment with eslicarbazepine acetate: Study BIA-2093-301.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Scientific Exhibition.
5. Sandsmark, D.K., Pelletier, C., Weber, J.D., Gutmann, D.H. *Mammalian target of rapamycin: Master regulator of cell growth in the nervous system*. Histol Histopathol 2007, 22(8): 895-903.
6. Kumar, V., Zhang, M.X., Swank, M.W., Kunz, J., Wu, G.Y. *Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways.* J Neurosci 2005, 25(49): 11288-99.
7. Wong, M. *Advances in basic and translational research in developing antiepileptogenic and neuroprotective treatments for epilepsy*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, AET Symposium.
8. Meikle, L., Pollizzi, K., Egnor, A., Kramvis, I., Lane, H., Sahin, M., Kwiatkowski, D.J. *Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: Effects on mTORC1 and Akt signaling lead to improved survival and function.* J Neurosci 2008, 28(21): 5422-32.
9. Merlin, L.R. *"TOR"rents of excitement over rapamycin's antiepileptogenic potential*. Epilepsy Curr 2008, 8(6): 163-5.
10. Zeng, L., Rensing, N.R., Wong, M. *The mammalian target of rapamycin signaling pathway mediates epileptogenesis in a model of temporal lobe epilepsy.* J Neurosci 2009, 29(21): 6964-72.
11. Rogawski, M.A. *The future of epilepsy treatment*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Lennox Lecture.
12. Dhir, A., Zolkowska, D., del Cid, B., Lossin, C., Murphy, R., Rogawski, M. *Rapid anticonvulsant action of a propofol prodrug administered by the intrapulmonary route in rats.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst 2.212.
13. Miller, J.M., Kustra, R.P., Vuong, A., Hammer, A.E., Messenheimer, J.A. *Depressive symptoms in epilepsy: Prevalence, impact, aetiology, biological correlates and effect of treatment with antiepileptic drugs.* Drugs 2008, 68(11): 1493-509.
14. Mulam, M., Sanderm, J.W. *Negative effects of antiepileptic drugs on mood in patients with epilepsy.* Drug Saf 2007, 30(7): 555-67.
15. Kalinin, V.V. *Suicidality and antiepileptic drugs: Is there a link?* Drug Saf. 2007, 30(2): 123-42.
16. Ettinger, A.B., Kustra, R.P., Hammer, A.E. *Effect of lamotrigine on depressive symptoms in adult patients with epilepsy.* Epilepsy Behav 2007, 10(1): 148-54.
17. Mazarati, A., Siddarth, P., Baldwin, R.A., Shin, D., Caplan, R., Sankar, R. *Depression after status epilepticus: Behavioural and biochemical deficits and effects of fluoxetine.* Brain 2008, 131(Pt. 8): 2071-83.
18. Mazarati, A.M., Pineda, E., Shin, D., Tio, D., Taylor, A.N,. Sankar, R. *Comorbidity between epilepsy and depression: Role of hippocampal interleukin-1beta*. Neurobiol Dis 2010, 37(2): 461-7.

19. Kanner, A.M. *Epilepsy and psychiatric disorders: The bi-directional co-morbidity*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst.
20. Kondziella, D., Asztely, F. *Don't be afraid to treat depression in patients with epilepsy!* Acta Neurol Scand 2008, 119(2): 75-80.
21. Richerson, G.B. *The serotonin axis: Shared mechanisms in seizures, depression and SUDEP.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Merritt-Putnam Symposium.
22. Kanner, A.M. *Epilepsy and mood disorders*. Epilepsia 2007, 48(9): 20-2.
23. Noebels, J.F. *Epilepsy and dementia: Converging mechanisms*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Merritt-Putnam Symposium.
24. Scarmeas, N., Honig, L.S., Choi, H. et al. *Seizures in Alzheimer disease: Who, when, and how common?* Arch Neurol 2009, 66(8): 992-7.
25. Amatniek, J.C., Hauser, W.A., DelCastillo-Castaneda, C. et al. *Incidence and predictors of seizures in patients with Alzheimer's disease*. Epilepsia 2006, 47(5): 867-72.
26. Minkeviciene, R., Rheims, S., Dobszay, M.B. et al. *Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy*. J Neurosci 2009, 29(11): 3453-62.
27. Vezzani, A., Ravizza, T., Nissinen, J., Kharatishvili, I., Vanzulli, I., Pitkänen A. *Brain inflammation in a rat model of post-traumatic epilepsy (PTE): Focus on the IL-1β system*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst 3.316.
28. Ye, Z.C., Sontheimer, H. *Cytokine modulation of glial glutamate uptake: A possible involvement of nitric oxide.* Neuroreport 1996, 7(13): 2181-5.
29. Vezzani, A., Conti, M., De Luigi, A., Ravizza, T., Moneta, D., Marchesi, F., De Simoni, M.G. *Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: Functional evidence for enhancement of electrographic seizures*. J Neurosci 1999, 19(12): 5054-65.
30. Viviani, B., Bartesaghi, S., Gardoni, F. et al. *Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases*. J Neurosci 2003, 23(25): 8692-700.
31. Vezzani, A. *The impact of neuroinflammation on neuronal excitability and excitotoxicity*. 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst IW.02.
32. Dhir, A., Naidu, P.S., Kulkarni, S.K. *Effect of cyclooxygenase inhibitors on pentylenetetrazol (PTZ)-induced convulsions: Possible mechanism of action.* Prog Neuropsychopharmacol Biol Psychiatry 2006, 30(8): 1478-85.
33. Freeman, J.M., Kossoff, E.H., Hartman, A.L. *The ketogenic diet: One decade later*. Pediatrics 2007, 119(3): 535-43.
34. Levy, R., Cooper, P. *Ketogenic diet for epilepsy.* Cochrane Database Syst Rev 2003, 3: CD001903.
35. Ginzberg, M., Watemberg, N., Levi, A. et al. *Ketogenic diet as antiepileptic therapy: A description of the clinical experience and the multidisciplinary approach at the metabolic-neurogenetic clinic at the Wolfson Medical Center.* Harefuah 2004, 143(3): 177-81.
36. Neal, E.G., Chaffe, H., Schwartz, R.H. et al. *The ketogenic diet for the treatment of childhood epilepsy: A randomised controlled trial.* Lancet Neurol 2008, 7(6): 500-6.
37. Caraballo, R.H., Cersósimo, R.O., Sakr, D., Cresta, A., Escobal, N., Fejerman, N. *Ketogenic diet in patients with myoclonic-astatic epilepsy.* Epileptic Disord 2006, 8(2): 151-5.
38. Kossoff, E, Patel, A., Pyzik, P., Rubenstein, J., Turner, Z. *Long-term health and seizure outcomes of children treated with the ketogenic diet.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst 1.258.
39. Schultz, R., Wilfong, A. *Effect of a high-fat formula-only ketogenic diet on plasma levels of lipids and lipoproteins in children.* 63rd Annu Meet Am Epilepsy Soc (Dec 4-8, Boston) 2009, Abst 1.278.