Chapter 11

Trace Elements, Antioxidant Enzymes and Free Carnitine Levels Among Epileptic Patients Treated with Valproate Monotherapy

Elżbieta Płonka-Półtorak, Tuomas Westermarck, Pekka Kaipainen, Markus Kaski and Faik Atroshi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/57613

1. Introduction

1.1. Epilepsy and oxidative stress

Epilepsy is a common chronic neurological disorder with a prevalence of 0, 4 – 1 % of the general population [1]. The highest incidence rates are in children and elderly. Epilepsy is characterized by recurrent unprovoked seizures, generalized or focal. The epileptic seizure is a clinical manifestation of transient excessive and hyper synchronous activity of neurones in the brain. It may include alterations of consciousness, motor or autonomic components or subjective sensory or psychic phenomena. An epilepsy syndrome is a complexity of signs and symptoms defining a unique condition. One of the most common syndromes is Juvenile myoclonic epilepsy accounting for up to 10% of all epilepsies [2].

Etiology of epilepsy in the majority is not identified [3]. Genetic defect or structural-metabolic disorder of the brain may be the cause of some chronic seizures. The commonest acquired causes of epilepsy include vascular diseases, tumours, trauma, and infections of the central nervous system [2]. However, the mechanisms of epileptogenesis are not well understood.

Experimental and human studies suggested that the homeostasis of trace elements and membrane lipid peroxidation due to increase of free radicals or decreased of antioxidant defence mechanisms have been causally involved in some forms of epilepsies. They were directly or indirectly implicated as taking part in the pathophysiology of neuronal excitability, neuronal excitotoxicity, seizure recurrence and its resistance to treatment with antiepileptic drugs [4].

Oxidative stress is a common pathogenic mechanism in neurodegenerative disorders. The central nervous system is particularly susceptible to reactive oxygen species (ROS) due to high oxygen demands of the brain, low concentration of endogenous antioxidants and concomitant accumulation of reactive iron. Furthermore, the abundance of polyunsaturated fatty acids and excess of predominant neurotransmitter glutamate, favour cell toxicity [5]. ROS can activate a self-accelerating vicious cycle leading to mitochondrial damage and neuronal cell death [6].

In epilepsy, the oxidative/antioxidative balance can have a role in both seizure controls and side effects of often life-long pharmacotherapy.

2. Pharmacotherapy of epilepsy-Valproic acid

There are a large range of antiepileptic drugs with different mechanisms of action, pharmacokinetics, pharmacology, and important side effects. Pharmacotherapy of epilepsy is symptomatic.

Valproic acid (VPA) which is an eight-carbon branched-chain fatty acid, is one of the most widely used effective antiepileptic drugs. The main mechanism of the action includes a blockade of sodium channels, activating calcium dependent potassium conductance and GABAergic effect [7]. VPA is metabolized by microsomal glucuronide conjugation, mitochondrial beta-oxidation and cytochrome P450-dependent omega-, (omega-1)-and (omega-2)-oxidation [8]. Therefore, an involvement of lipid peroxidation seems to be probable during pharmacotherapy with VPA.

Serious side effects are relatively rare but include fatal hepatotoxicity and acute haemorrhagic pancreatitis. They occur mainly in children on polypharmacy and those with organic brain disease. Hyperammonaemic encephalopathy has been reported in patients with urea cycle disorder. Benign elevation of liver enzymes is common during valproate therapy and dose depended. Thrombocytopenia and other haematological abnormalities should be controlled. Other troublesome adverse effects are weight gain, gastrointestinal disturbances, hair loss and tremors. Hormonal disturbances with polycystic ovary syndrome and risk of teratogenicity, including a 1 to 3% risk of neural tube defects, make the use of VPA in some women undesirable [7].

In numerous studies there was found to be an imbalance in oxidative status of the patient with epilepsy treated with VPA [9].

3. Role of trace elements and antioxidant enzymes in epilepsy

3.1. Iron

In several neurodegenerative diseases, iron accumulates in brain tissues. Since post-mortem examinations cannot distinguish whether iron accumulation is a cause or consequence of brain

http://dx.doi.org/10.5772/57613

damage, it is necessary to manipulate iron to assess its causal role. In the animal model of epilepsy, iron supplementation increased damage in various brain regions, and a tight relationship between iron and zinc in micro gliosis was found [10]. In general, iron is kept safe by binding itself to protein; transported in form of transferrin-bound iron or stored in form of ferritin. The liberation of free iron can augment generation of active free radicals and it appears to play a crucial role in the posttraumatic epilepsy [11]. Iron deposition results in tissue damage by either directly damaging cells or changing the cellular environment so that it is more susceptible to toxins or other pathologic processes. On the other hand, iron is a cofactor of catalase (CAT), which plays a role in antioxidant defence systems by catalysing the decomposition of hydrogen peroxide. The proper balance of iron without excessive supplementation is very important for oxidant status.

The surrogate markers of iron status may be non-transferrin bound iron (NTBI). There was found an increase in NTBI in patients treated due to epilepsy with VPA [12].

3.2. Selenium, cooper, zinc

The trace elements selenium (Se), cooper (Cu) and zinc (Zn) are important cofactors of antioxidant enzymes such as superoxide dismutase (Cu-SOD, Zn-SOD), glutathione peroxidise (GPX) as well as protein with antioxidant properties, ceruloplasmin (CRL, copper-binding protein). SOD and GPX play a predominant role as free radical scavengers in the brain tissue, whilst CAT is deficient [13]. SOD and GPX are also important for detoxification of xenobiotics, and may be involved in the oxidative injury caused by antiepileptic drugs [14].

Results of various studies on trace elements levels and activities of main antioxidant enzymes during pharmacotherapy of epilepsy are conflicting. A selected bias of patients and different laboratory methods might be responsible, as well as the influence of lifestyle with consumption of natural antioxidants or their supplementation [4, 15, 16].

A decrease in the trace elements selenium and copper was reported in epileptic patients receiving sodium valproate [17]. One of the main selenium status marker is plasma glutathione peroxidise (GPX3). The product of plasma SOD (pSOD) activity, H_2O_2, is the major substrates for GPX3. An involvement of lipid peroxidation seems to be probable and the elevated activity of pSOD in some studies may be explained by this induction. Significant effects of duration of VPA therapy, activity of seizures and gender were found on Zn, pSOD, and erythrocyte SOD (eSOD) levels [4, 9]. Also in prospective studies [18, 19] were reported increased levels of eSOD in epileptic children after implementation of VPA treatment. Some other authors did not find a significant difference in enzyme activity or even a reduced level of pSOD was found in young people with epilepsy treated using valproate [20].

pSOD is a sensitive index of Cu status, while plasma Cu is not a reliable marker of copper status [21]. Zinc supplements can decrease SOD activity, primarily due to the antagonistic relationship between high zinc intakes and copper absorption [22, 23]. A few authors reported lower or normal Zn concentrations in persons with epilepsy [24, 25]

4. Carnitine and cellular energy

L-carnitine is the key factor in mitochondrial beta oxidation of fatty acids for the generation of metabolic energy. Apart from carrying the long-chain fatty acids into the mitochondrial matrix, it takes part in transporting from peroxysomes into mitochondria the products of oxidation of very long-chain fatty acids and in removing from mitochondria medium and short-chain fatty acids, which can be toxic at a high level. As a donor of acetyl group, it participates in the synthesis of neurotransmitter acetylocholine. It also takes part in the reaction of detoxication, including the removal of some drugs, and in chelation of iron [26].

L-carnitine is synthesized in the liver, kidneys and brain from essential amino acids lysine and methionine, with participation of the vitamins C, B_6, PP, and iron. The main source of L-carnitine in the diet is meat and dairy products. When the diet is rich in the aforementioned products and there are no liver and kidney diseases, the risk of carnitine deficiency is low. Bioavailability of carnitine from medical preparations is only ca. 20% [27].

Carnitine deficiency can result from fatty acid oxidation disorders, organic acidemias, renal insufficiency, and treatment with some drugs, as valproic acid. The clinical symptoms of L-carnitine deficiency involve brain with enhanced risk of hypoketonic-hypoglycemic and hepatic encephalopathy, or skeletal and cardiac myopathy. Carnitine deficiency in case of fatty acids oxidative disorders can cause epileptic seizures. The seizures may result from cerebral bioenergetic failure associated with acute episodes of hypoglycemic, hypoketotic encephalopathy, or hypoxic-ischemic encephalopathy due to cardiac arrhythmias and/or cardiomyopathy [28].

In numerous studies, reduced carnitine levels were found during VPA therapy, especially with prolonged use and with high dosage levels [29]. The mechanism of this may include: 1) the formation of valproylcarnitine, 2) the reduction of tubular reabsorption of carnitine in the kidneys, 3) the inhibition of selected enzymes, which take part in biosynthesis of carnitine, 4) the inhibition of the membrane carnitine transporter and 5) the impairment of recycling of carnitine from long-chain acylcarnitines by the VPA-induced decrease of mitochondrial free Co-A level. Deficiency of carnitine is one possible mechanism which explains the VPA induced hepatotoxity. Carnitine depletion can impair the urea cycle (by influence on its enzymes) and cause accumulation of ammonia, what can be found in hepatic failure [30]. The impairment of beta-oxidation can shift the metabolism of VPA toward predominantly peroxisomal gamma-oxidation, resulting in excessive production and accumulation of toxic metabolite 4-en-VPA. It is postulated that carnitine supplementation may increase the beta-oxidation of VPA and limit production of its toxic metabolites. Carnitine inhibits free radicals generation preventing the impairment of fatty acid betaoxidation in mitochondria and protects tissues from damage by repairing oxidized membrane lipids [31].

http://dx.doi.org/10.5772/57613

5. New therapeutic approaches

Some of side effects of therapy with VPA have been suggested by alteration the homeostasis of trace elements and antioxidants. Seriously increase membrane lipid peroxidation at the expense of protective antioxidants; this may lead to an increase in the frequency of seizures and an idiosyncratic drug effect.

Adequate trace elements and antioxidants supply is essential for normal brain functions, and is particularly important for protection against neurological disorders. To elucidate the mechanism of action such substances in the brain should result in new safe therapeutic approaches.

Author details

Elżbieta Płonka-Półtorak[1], Tuomas Westermarck[2], Pekka Kaipainen[2], Markus Kaski[2] and Faik Atroshi[3]

1 Antiepileptic Outpatient Clinic, Provincial Hospital No. 2, Lwowska, Rzeszow, Poland

2 Rinnekoti Research Center, Espoo, Finland

3 Pharmacology & Toxicology, University of Helsinki, Finland

References

[1] http://www.who.int/mediacentre/factsheets/fs999/en/

[2] Shorvon S. Epilepsy. ONL Series. Oxford Neurology Library. Oxford University Press, 2009.

[3] Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res 2009; 85(1):31-45.

[4] Hamed S, Abdullah M. Trace elements and electrolytes homeostasis and their relation to antioxidant enzyme activity in brain hyperexcitability of epileptic patients. J Pharmacol Sci 2004; 96:349-59.

[5] Naziroglu M. (New molecular mechanism on the activation of TRPM2 channels by oxidative stress and ADP-ribose. Neurochem Res 2007; 32:1990-2001.

[6] Patel M. Mitochondrial dysfunction and oxidative stress: cause and consequence of epileptic seizures. Free Radic Biol Med 2004; 37(12):1951–1962.

[7] Panayiotopoulos CP. Pharmacopoeia of prophylactic antiepileptic drugs. In: The epilepsies: seizures, syndromes and management. Bladon Medical Publishing, Oxfordshire (UK) 2005;pp 504-506.

[8] Perucca E. Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. CNS Drugs 2002; 16:695-714.

[9] Płonka-Półtorak E, Zagrodzki P, Chłopicka J, Bartoń H, Westermarck T, Kaipainen P, Kaski M, Atroshi F. Valproic acid modulates superoxide dismutase, uric acid-independent FRAP and zinc in blood of adult epileptic patients. Biol Trace Elem Res 2011;143(3):1424-34.

[10] Shoham, S, Youdim MBH. Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases. Cell. Mol. Biol 2000; 46: 743–760.

[11] Choi, BH. Oxygen, antioxidants and brain dysfunction. Yonsei Med J 1993; 34(1):1–10.

[12] Ounjaijean S, Westermarck T, Partinen M, Plonka-Poltorak E, Kaipainen P, Kaski M, Fucharoen S, Srichairatanakool S, Atroshi F. Increase in non-transferrin bound iron and the oxidative stress status in epilepsy patients treated using valproic acid monotherapy. Int J Clin Pharmacol Ther 2011; 49(4): 268-7

[13] Halliwell B, Gutteridge JM. Free radicals in biology and medicine. Oxford University Press,1999, Oxford.

[14] Maertens P, Dyken P, Graf W, et al. Free radicals, anticonvulsants, and the neuronal ceroid-lipofuscinoses. Am J Med Genet 1995; 57:225-228.

[15] Sudha K, Rao AV, Rao A. Oxidative stress and antioxidants in epilepsy. Clin Chim Acta 2001; 303:19-24.

[16] Cengiz M, Yüksel A, Seven M. The effects of carbamazepine and valproic acid on the erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children. Pharmacol Res 2000;41:423-425

[17] Armutcu F, Ozerol E, Gurel A, et al. Effect of long-term therapy with sodium valproate on nail and serum trace element status in epileptic children. Biol Trace Elem Res 2004; 102:1-10.

[18] Yiş U, Seçkin E, Kurul SH, Kuralay F, Dirik E. Effects of epilepsy and valproic acid on oxidant status in children with idiopathic epilepsy. Epilepsy Res 2009; 84:232-237

[19] Yüksel A, Cengiz M, Seen M, Ulutin T Erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children with valproate and carbamazepine monotherapy.J Basic Clin Physiol Pharmacol 2000; 11:73-81

[20] Solowiej E, Sobaniec W. The effect of antiepilepticdrug therapy on antioxidant enzyme activity and serum lipid peroxidation in young patients with epilepsy. Neurol Neurochir Pol 2003; 37:991-1003

[21] Harvey LJ, McArdle HJ. Biomarkers of copper status: a brief update. Brit J Nutr 2008; 99:S10–S13

[22] Mariani E, Mangialasche F, Feliziani FT, et al. Effects of zinc supplementation on antioxidantenzyme activities in healthy old subjects. Exp Gerontol 2008; 43:445-451

[23] Hughes S, Samman S. The effect of zinc supplementation in humans on plasma lipids, antioxidant status and thrombogenesis. J Am Coll Nutr 2006; 25:285-291

[24] Barbeau A, Donaldson J. Zinc, taurine, and epilepsy. Arch Neurol 1974; 30: 52-58

[25] Higashi A, Ikeda T, Matsukura M, Matsuda I. Serum zinc and vitamin E concentrations in handicapped children treated with anticonvulsants. Dev Pharmacol Ther 1982; 5:109-113

[26] Arrigoni-Martelli E, Caso V. Carnitine protects mitochondria and removes toxic acyls from xenobiotics. Drugs Exp Clin Res 2001; 27: 27–49.

[27] Verrotti A, Greco R, Morgese G, Chiarelli F. Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. Int J Clin Lab Res 1999; 29(1):36-40.

[28] Tein I, Xie ZW. Reversal of valproic acid-associated impairment of carnitine uptake in cultured human skin fibroblasts. Biochem Biophys Res Commun1994; 28, 204(2): 753-8.

[29] Płonka-Półtorak E, Zagrodzki P, Chłopicka J, Bartoń H, Westermarck T, Kaipainen P, Kaski M, Atroshi F. Valproic acid modulates superoxide dismutase, uric acid-independent FRAP and zinc in blood of adult epileptic patients. Biol Trace Elem Res. 2011; 143(3):1424-34

[30] Lheureux PE, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity-what is the evidence? Crit Care 2005; 9(5):431-40

[31] Gulcin I. Antioxidant and antiradical activities of L-carnitine. Life Sci 2006; 78:803-811.

IntechOpen