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REVIEW ARTICLE

POLYUNSATURATED FATTY ACIDS IN IDIOPATHIC EPILEPSY TREATMENT IN DOGS

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Abstract. Epilepsy is both a primary disease and secondary sign of various neurological and metabolic disorders. Idiopathic epilepsy could be burdensome in its course. It requires often a multidrug therapy, that can lead to serious side effects. One of the supportive antiepileptic therapies is a proper diet. It is believed, that polyunsaturated fatty acids (PUFAs) give the chance of life quality improvement in dogs with idiopathic epilepsy.

Key words: PUFA, diet, idiopathic epilepsy, dog

Epilepsy is the most common chronic neurological disorder, affecting between 0.5 to 5.7% of the canine population. It is the sign of the increased brain electric activity. Attacks are characterised by separate, recurrent episodic disorders of movement, sensation, behaviour, perception and mentation. First attack occurs

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usually between 6 month and 5 year of life [Charalambous et al. 2014]. The aim of the therapy is shortening of the attack time, easing their course, and most importantly – limiting incidence number to the minimum. In the idiopathic epilepsy course cluster seizures and status epilepticus can be observed which directly threaten animal's life.

The pathogenesis of an epileptic seizure entails: (a) a decreased level of gamma-aminobutyric acid (GABA – the chief inhibitory neurotransmitter in the brain) in cerebrospinal fluid (CSF); and (b) imbalance between neural stimulation and inhibition processes [Kitajka et al. 2004, Basselin et al. 2009]. What was observed in dogs with epilepsy was an increase in glutamate (GLU) concentration in the CSF, higher sensitivity of NMDA receptor (N-methyl-D-aspartate receptor), lower levels of gamma-aminobutyric acid (GABA), and decreased GABA receptor sensitivity, which boosts the excitability of neurons in the brain [Kersten et al. 2001]. Other neurotoxic substances released during status epilepticus probably include aspartate, free fatty acids, arachidonic acid, and free radicals.

The use of anti-epileptic drugs, particularly in polytherapy, causes serious side effects. Therefore, research is underway to explore the influence of diet on the quality of life and a reduced number of seizures in dogs. The ketogenic diet leads to mild acidosis, during the course of which there ensues the inhibition of NMDA receptor caused by Mg^{2+} ions and thereby reduced neuronal excitability [Kitajka et al. 2004]. Other studies have shown an increased activity of glutathione peroxidase (one of the antioxidant enzymes) in the hippocampus. With respect to the nutritional factor – omega-3 fatty acids, it was found that a deficiency of this nutrient may contribute to the occurrence of convulsions [Rao et al. 2007a, 2007b]. Omega-3 fatty acids may improve the GABAergic transmission in epileptic animals by stimulating the formation of new hippocampal interneurons or change the structure of calcium-binding proteins [Cysneiros et al. 2010]. There is a documented case of canine idiopathic epilepsy where the frequency of seizures was reduced by supplementing the phenobarbital treatment with a diet rich in omega-3 fatty acids [Matthews et al. 2012]. Furthermore, the use of omega-3 acids improved neuroprotection [Farias et al. 2008] and increased the number of positive parvalbumins in hippocampal neurons in rats suffering from epilepsy. This suggests that omega-3 acids contribute to plastic changes in the brain [Ferrari et al. 2008]. However, there is no explicit explanation of omega-3 acids' independent therapeutic effect or of them being used as an element which supports the treatment of canine epilepsy [Rapoport 2003].

Polyunsaturated fatty acids (PUFAs), such as linoleic, linolenic, and arachidonic acids, are crucial structural components of the neuronal membrane [Hostetler et al. 2006]. About 60% of the brain's dry weight consists of fatty compounds, and about 30% of this fat is made up of polyunsaturated fatty acids (PUFAs)

[Kodas et al. 2004]. Linoleic and arachidonic acids are the precursors of pro-inflammatory compounds [Hong et al. 2003]. Inflammation is a defense reaction of tissues to damage. Studies on the inflammatory mediators produced from the arachidonic acid (AA) led to the identification of PUFA derivatives with the anti-inflammatory potential, for example prostaglandins and leukotrienes [Taha et al. 2010]. Inflammatory mediators include lipoxins and resolvins. DHA is also a precursor for other inflammatory mediators: neuroprotectin and maresin [Xiao et al. 1997].

EPA and DHA have been detected in human neutrophils. They curb the production of pro-inflammatory prostaglandin E2 (PGE2), depending on the dose. It is believed that there is a link between the occurrence of seizures and the secretion of proinflammatory cytokines. For example, convulsions or status epilepticus (SE) induced by chemical or electrical stimulation increase the expression of pro-inflammatory cytokines such as interleukin IL-1 b, IL-6 [Voskuyl et al. 1998]. Drugs that reduced the production of proinflammatory cytokines helped to stop convulsions [Vezzani et al. 1999]. Perhaps omega-3 acids also have such properties.

The lipid structure of omega-3 fatty acids makes them pass through the blood-brain barrier. Omega-3 and omega-6 acids have versatile properties. One example is their active contribution to the formation of neurons. The formation of neurons is modulated by neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) [Lee et al. 2002, Cysneiros et al. 2010]. It has been shown that BDNF resulted in the differentiation and survival of neurons in the hippocampus and cerebral cortex of a rat [Ferrari et al. 2008]. It was observed that the exclusion of omega-3 acids from diet for 15 weeks lowered the DHA levels of the frontal cortex and decreased the expression of BDNF in the cortex. In addition, the in vitro administration of DHA to the rat's frontal cortex astrocytes induced the expression of BDNF [Rao et al. 2007a, 2007b].

Myelin integrity is crucial for the proper functioning of the axons of the nervous system. Any breaks or damages to myelin may cause numerous neural disorders. Unsaturated fatty acids play a vital role during myelin synthesis. Deficiency of PUFAs at this stage can lead to myelin degeneration [Voskuyl et al. 1998, Taha et al. 2010].

Generally, essential unsaturated fatty acids, including DHA, influence brain functionality. They modify the fluidity of cell membrane, the activity of membrane enzymes, and the number and affinity of receptors. They also have an effect on the functioning of neuronal ion channels and the production of neurotransmitters [Xiao et al. 1997, Sovik et al. 1998, Lauritzen et al. 2000]. These properties help to relieve the symptoms of epilepsy. PUFAs and phospholipids may offset

the detrimental effects of substances that cause seizures. Iron increases lipid peroxidation and thereby leads to the loss of integrity in the biological membranes. As previously mentioned, omega-3 acids may have an impact on the fluidity of cell membrane. The index of membrane fluidity depends on the ratio of PUFAs and cholesterol. It is commonly recognized that cholesterol decreases the index of cell membrane fluidity which influences the activity of ion channels and receptor functions as well as on dopamine release. The mechanism by which omega-6 or omega-3 acids are able to reduce cholesterol levels in the blood or in neuronal membrane is still unclear, although there are some hypotheses [Zimmer et al. 2000]. PUFAs and phospholipids can control changes in the metabolism of neuronal membrane phospholipids. In turn, changes in the metabolism of phospholipids may increase the incidence of amino acids which stimulate receptors toward the epileptic seizure. PUFAs may induce neuroprotection in the brain [Lauritzen et al. 2000, Farias et al. 2008] PUFAs contribute to the expression of genes in the nuclear proteins of PPAR receptors. PPARs play a key role in the regulation of the metabolic reactions of lipids and the regulation of glucose homeostasis in the body [Hostetler et al. 2006].

Matthews et al. [2012] conducted a study on dogs with idiopathic epilepsy, supplementing them with omega-3 acids. Fifteen dogs were fed triple-purified omega-3 acids. They contained 400 mg of eicosapentaenoic acid, 250 mg of docosahexaenoic acid, and 22 mg of vitamin E in 15 ml. The dose was 15 ml per 10 kg once a day for 12 weeks. Then, the dogs were fed olive oil as a placebo for 12 weeks. In this study, PUFA supplementation did not yield promising results. It is not known whether the subsequent administration of olive oil had any impact on the results. The dose and duration of PUFA administration requires further research.

There were many studies aimed to develop a treatment of idiopathic epilepsy in dogs. So far safe and effective treatment has not been developed. Treatment and reduction of the symptoms of epilepsy in dogs most often amounts to deliver drugs. Based on the data from the current literature, it appears that the attempt to use alternative methods for idiopathic epilepsy, e.g. dietary supplementation of polyunsaturated fatty acids can generate beneficial results [Sovik et al. 1998, Scorza et al. 2009]. However it requires further research with the use of greater number of breeds of dogs (especially susceptible to this disease entity) and more numerous experimental material.

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WIELONIENASYCONE KWASY TŁUSZCZOWE W TERAPII PADACZKI IDIOPATYCZNEJ U PSÓW

Streszczenie. Padaczka to choroba zarówno o podłożu pierwotnym, jak i wtórny objaw różnych schorzeń neurologicznych i zaburzeń metabolicznych. Padaczka idiopatyczna bywa uciążliwa w swoim przebiegu. Nierzadko wymaga stosowania terapii wielolekowej, która niesie ze sobą ryzyko poważnych skutków ubocznych. Jedną z możliwości wspierania leczenia przeciwpadaczkowego jest odpowiednia dieta. Wydaje się, że wielonienasycone kwasy tłuszczowe (WNKT) dają szansę na poprawę jakości życia u psów z padaczką idiopatyczną.

Słowa kluczowe: WNKT, dieta, padaczka idiopatyczna, pies

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