Research and Report

Progress in the treatment of epileptic brain injury with non-traditional antiepileptic drugs

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Epilepsy , with different etiologies and variable location of the epileptogenic zones (EZs) ， is a complex and highly impactful neurological disease. According to the World Health Organization report, there are about 50 million epilepsy patients around the world, and about 9 million in China. Meanwhile, disease incidence is increased at the rate of 400,000 every year, including children accounting for about 2/3[1]. Both clinical and basic studies have shown that long-term recurrent seizures during development can cause cognitive defect, affective disorders and abnormal behavior. Therefore, immediate medical attention and long-term therapy are necessary. Currently, a large number of anti-epileptic drugs (AEDs) are available for seizure treatment, but for refractory epilepsy, surgical treatment is mainly used . Surgical treatment approaches for refractory epilepsy can be classified into three main categories: open surgery, neuroablation, and neuromodulation[2].

Although traditional anti-epileptic drugs have certain curative effect, but the side effect is so large that some children cannot tolerate. As for surgical treatment not only has limited indication sign but also certain risk. Unfortunately, 30%–40% of epilepsy patients become medically refractory and fail to respond to current medical treatments[3].

Therefore, the mechanism of convulsive brain injury need to be further studied. To search for new anti-epileptic ways to treat epilepsy with minimal side effects become a hot topic at home and abroad. Here we provide an overview of studies using the ketogenic diet（KD）， melatonin（MEL）and leptin in treating epilepsy .

Keywords: anti-epileptic, ketogenic diet, melatonin, leptin

1. **ketogenic diet (KD**)

The ketogenic diet (KD), a high-fat but low-carbohydrate, adequate-protein alimentary Regimens. In 1921, it was first designed as an anticonvulsant dietetic protocol[4]. In late 1990s, KD was effective on treating the child patients with intractable epilepsy with good tolerance, especially in epileptic children not suitable for surgery or in children with drug resistant epilepsy[5]. While because of gianing benefits from the therapy method and the number of patients with refractory epilepsy is not declining,

despite all the new AEDs now available[6, 7], KD became a common treatment with resurgence in popularity.

In recent years, a large amount of studies have reported that the KD has a good effect on controlling seizures[8]with fewer side effects, has its great advantage than traditional anti-epileptic[9]. Suo C et al. reported that after 3, 6 and 12 months' therapy with KD, 35.0%, 26.2% and 18.6% showed >50% seizure reduction, including 20.8%, 13.6% and 10.7% seizure free, respectively[10]. Although, it is a highly effective treatment，the actual mechanism by which the KD helps suppress epilepsy remains unclear despite decades of research. What's more, the problem we will meet is that any long-term risks through using KD , like growth problems[11], Kidney stones[12], serum cholesterol and triglyceride levels may increase as well[13].

More basic researches showed that it mainly affects the body's metabolism, neurotransmitters, ion channels, and to a certain extent, plays a neuro-protective role. For example, Metabolites such as ketone bodies and polyunsaturated fatty acids (PUFAs) in KD therapy have anti-epileptic effects[14, 15]. Though, dietary therapies are often perceived as natural treatments for disease. We should spend efforts and scientific talent to figure out how it works.

2. Melatonin（MEL）

Melatonin(MEL, N-acetyl-5-methoxytrypt amine), a pleiotropic neurohormone , was first extracted from cattle by Aron Lerner et al. in the 1950s. In human beings, it is mainly secreted by the pineal gland and partially by other peripheral organs that are widely distributed, including in the retina, bone marrow, gut, gonads , and immune-competent cells[16] . Meanwhile, it is released in a circadian pattern with peak concentrations at night and can maintain circadian rhythm，eliminate free radicals，promote sleep, regulate immune response, delay senescence, inhibit cancer and other physiological functions[17].

In addition, in recent years, a large number of studies have proved that MEL plays a neuroprotective role in neonatal ischemia and hypoxia, alzheimer's disease and other neurological diseases. It is considered as a potential intervention for brain injury[18, 19]. In clinical practice，it has been widely used to treat sleep disturbances.

Research has suggested an anti-epileptic role of melatonin[20].

However studies investigating the long-term effects of melatonin are still lack as well as the function mechanism. Rudeen et al.[21]showed that pinealectomy can cause seizures that could be reverted by the pre-treatment with melatonin ， while melatonin is released by pineal gland and has a possible anti-convulsive effect by the endogenously-produced melatonin [22]. Schapel et al.[23] reported that melatonin secretion increased in untreated patients with active epilepsy compared with the healthy. The main mechanism of anti-epileptic is that melatonin has remarkable antioxidant properties and inhibition of excitatory intoxication events[22, 24] It might be worth pursuing that melatonin will be used in clinic in combination with other traditional therapies.

3. Leptin

Leptin, an adipocyte peptide hormone of 16-kDa, is synthesized and secreted mainly by the adipose tissue. It has structural homology with long-chain helical cytokines including IL-6, IL-11, IL-12, and oncostatin M[25]. Leptin was first identified

in obese(ob) mice in 1994 using molecular cloning techniques[26].

For recently years, multiple additional effects have been described , such as food intake and metabolism regulation, endocrine function，body weight[27]. Leptin exhibits neuroprotective effects in animal models of kainic acid- or pilocarpine induced status epilepticus[28, 29]. Neuroendocrine function is mainly dominated by long form of the leptin receptor[30]. Leptin levels were elevated after treatment with VPA(valproic acid) for epilepsy[31]. Kinzig et al.'s research[32] and several researches[33, 34] demonstrate there was a rise in leptin after KD. However, studies by Danielle et al [35]reported that leptin decreased during treatment with the KD . Therefore, further elucidation and better understanding of the molecular mechanism of neuroprotective effects of KD, leptin as well as other function may yield new insights into the pathophysiology of epilepsy and is more conducive to search for new treatment strategies. While the choice of the anti-epileptic must be made on an individual basis considering the patient's age, family circumstances,and severity and type of epilepsy. Physicians should be aware of these findings and would have to consider adjusting different patients with proper therapy. In particular, this adjustment would be necessary if further mechanisms will be find out.

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