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Glucosamine Affects Epileptic Activity Through the Regulation of Brain Energy Metabolism

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ABSTRACT

Epilepsy is a group of electro clinical syndromes characterized by abnormal, highly synchronized neuronal discharges, resulting in transient brain dysfunction, mainly manifested by seizure-like limb twitching, sensory abnormalities, mental, cognitive, and emotional disturbances with or without impaired consciousness. Currently, the prevalence of epilepsy exceeds 60 million worldwide and is a public health issue of widespread concern due to the high disability and mortality rates of epilepsy disorders.

Keywords: Epilepsy, Seizures, Glucosamine, Mitochondrial disorders, Neurotransmitters.

ABOUT THE STUDY

Seizures are a process of energy accumulation, eruption and depletion, accompanied by the generation, propagation and termination of epileptic discharges, the energy source required for the epileptic seizure process is mainly provided by Adenosine Tri Phosphate (ATP) produced by mitochondria [1]. Mitochondrial disorders often lead to seizures, and seizure-related energy expenditure can lead to impairment of mitochondrial function, which are mutual targets and ultimately lead to epileptic pathological damage and recurrent spontaneous seizures [2].Therefore, brain energy metabolism has become a key target and an important therapeutic tool for epilepsy treatment, but the mechanisms based on which brain energy metabolism regulates seizures and the progression of epilepsy formation are poorly addressed [3].

The mechanism of seizure termination is still unclear, and possible mechanisms include altered ion channels, neurotransmitters and progressively depleted energy metabolism [4]. Researchers have suggested that seizure termination is related to the "metabolic dynamics" of the brain and that astrocyte dysfunction may be a major factor [5]. However, regardless of the specific mechanisms of termination, the ability of these mechanisms to meet the energy demands of the highly synchronized electrical activity of neurons is crucial for the termination of epilepsy [6]. Mismatch between energy demand and supply or energy depletion is the main mechanism of spontaneous termination of epilepsy. Therefore, control of neuronal electrical activity is the primary goal of epilepsy control [7]. Recently, reported that mitochondria

play a key role in neurotransmitter synthesis, calcium homeostasis, redox reactions, reactive oxygen species production, and neuronal survival, and seizure induced energy expenditure may lead to mitochondrial dysfunction, altering calcium homeostasis, reactive oxygen species production, ion-Channel permeability, and neurotransmitter transport proteins, and decreasing neuronal membrane potential. Mitochondrial dysfunction inhibits the function of interneurons, leading to an imbalance of excitatory and inhibitory properties in the brain, destabilizing neural networks and eventually leading to recurrent seizures [8].

Glucosamine is an amino monosaccharide characterized by its small molecular weight and monomolecular structure, widely distributed in human tissues and playing an important role in cell membranes and other tissue structures [9]. In the extracellular matrix, Glucosamine enters chondrocytes mainly by diffusion [10]. Glucose transporter protein is used to facilitate glucose transport and to synthesize aminoglycans and then proteoglycans through chondrocytes [11]. Glucosamine is a dietary supplement widely used to promote joint health. Recent studies have shown that Glucosamine has anti-tumour, anti-inflammatory, antioxidant and anti-allergic effects [12]. Glucosamine also plays a neuroprotective role in a variety of central nervous system disorders, including Multiple sclerosis, Encephalomyelitis, Learning memory impairment, and Ischemic brain injury [13].

Glucosamine may affect multiple protein signalling pathways by increasing glucose uptake by the amino Hexose Biosynthesis Pathway (HBP) and lead to insulin resistance and elevated blood glucose levels [14]. Although the HBP pathway has been extensively studied in insulin-sensitive tissues, the effect of increased HBP activity on insulin sensitivity in the brain remains relatively unknown reported that Glucosamine induced increased levels of protein kinase B (Akt) phosphorylation in brain tissue and improved astrocyte Endoplasmic Reticulum (ER) stress capacity [15]. In addition, Glucosamine comes by enhancing HBP flux and increasing energy uptake by neurons, which may be one of the neuroprotective mechanisms of CNS injury [16]. Brain energy metabolism has a direct correlation with seizure generation, propagation and termination [17]. However, studies on whether Glucosamine affects epileptic activity have not been addressed [18]. We studied the effects of Glucosamine on acute lithium chloride-pilocarpine and PTZ models and chronic PTZ models of epileptic seizures and electrical activity. Glucosamine was administered at doses of 0.5, 1.0 and 2.0 g/Kg for 3 days and measured 2 h after the last gavage [19]. The results showed that 2.0 g/Kg of Glucosamine significantly prolonged the acute epileptic seizures and seizure duration induced by lithium chloride-pilocarpine and PTZ, shortened the latency of the first seizure, increased the susceptibility of epileptic seizures to termination, and increased the energy expenditure during epileptic seizures [20].

Glucosamine rapidly activates Akt signalling in astrocytes, increasing the amino Hexose Biosynthetic Pathway (HBP) and endoplasmic reticulum stress, thereby increasing ATP and glucose uptake and utilization [21]. We measured the expression of phosphorylated Akt and Akt in the hippocampus of epileptic rats with different intervention modalities [22]. The results suggest that 2.0 g/Kg of Glucosamine exacerbates epileptic seizures and electrophysiological activity, which may be achieved by activating the Akt signalling pathway rather than directly affecting blood glucose in the pilocarpine-induced epileptic seizure model [23]. Our previous study confirmed that the expression level of phosphorylated Akt increases after epileptic seizures and that recombinant human insulin-like growth factor promotes hyper phosphorylation of Akt and increases hippocampal excitability, promoting epileptic seizures and progression. Either insulin-like growth factor receptor inhibitor (PPP) or Akt antagonist inhibits Akt phosphorylation and reduces epileptic seizures [24].

High Frequency Oscillations (HFO), consisting of 80-200 Hz EEG waves and 200-600 Hz fast waves, are frequently present in the EEG of epileptogenesis and Seizures and are usually considered to be associated with primary epileptic foci [25]. However, there is also evidence that 80-200 Hz waves activate specific neuronal networks, which may be markers of epileptic seizures and severity. Our study shows that conventional doses of Glucosamine (2.0 g/Kg) promote lithium chloride-pilocarpine-induced seizure continuity by enhancing high-frequency electrophysiological activity [26]. We speculate that excessive activation of p-Akt by 2.0 g/Kg of Glucosamine may lead to endoplasmic reticulum stress, increase energy supply during epileptic seizures, and lead to less easy termination of epileptic seizures, which may be the main reason why 2.0 g/Kg of Glucosamine led to exacerbated seizure activity [27].

CONCLUSION

In summary, our findings suggest that different doses of Glucosamine have different effects on seizure activity. 2.0 g/Kg Glucosamine significantly prolonged epileptic seizure duration and increased epileptic seizure sensitivity and severity in mice through activation of Akt signalling. The results of the study provide evidence for the prudent use of Glucosamine in epileptic patients.

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