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The behavior change effect of levetriacetam in absence seizure

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Abstract. The absence seizure is characterized by loss of consciousness and appears as a 3-5 Hz spike wave like discharge in electroencephalography (EEG) recording. Levetiracetam mainly works on the SV2A molecule, which can mediate neurotransmitter release. Compared with other antipsychotics, levetriacetam has shown great tolerance, fewer side effects and great efficacy. However, levetriacetam may alter the patient's cognition and behavior in two different directions, enhance the cognition or become more aggressive. This change does not relate to the dose intake or other factors, it may be associated with the personal trait dopaminergic related gene. One possible explanation for this is that the dopaminergic related gene that can impact a person's trait can determine the adverse effect of levetriacetam. Understanding the relationship between the levetiracetam (LEV), absence seizure and behavior change can improve the safety of LEV modification, in this paper, there is the discussion about the role of the dopamine in the absence seizure, LEV pharmocology and behavior change.

Keywords: absence seizure, levetriacetam, behavior change, dopaminergic.

1. Introduction

The absence seizure can produce a brief loss of consciousness, eyelid fluttering or myoclonic jerk usually found during unconsciousness [1] and it can be characterized by detecting the 3-5Hz spike-wave like discharges (SWDs) in electroencephalography (EEG) recording [2]. In contrast, the consciousness may not be impacted by an atypical absence seizure [1]. Based on Hughes, the childhood form of absence seizure, the average duration was 9s for the absence, which means they are loss of awareness, staring, 3-Hz eyelid movements. He also indicates that 59% juvenile form patients are female, with average age of onset of 12 years old and 29% of the patients have family history [3]. However, 30% to 40% of childhood absence epilepsy patients have tonic-clonic seizures and 80%-70% of juvenile absence epilepsy patients also suffer from tonic-clonic seizures [4]. Besides, the typical absence seizure shows a prominent photosensitivity and polyspike discharges, which refers a greater possibility of progression to juvenile myoclonic epilepsy [4]. The cognition functions that are impacted by an absence seizure include motor function, decision making, memory and verbal response [1].

According to Poleon and Szaflarski, the levetiracetam (LEV), clabazam and ethosuximide can suppress photosensitivity [5]. Besides, compared with other first line anticonvulsants, the levetiracetam has relatively favorable side effect profile and a favorable tolerability profile [6] and this shows its ability to enhance the cognition function [6]. However, LEV can trigger a change in behavior and person's trait, and the symptom of those changes may be associated with dopaminergic related gene [7]. Find the relationship between LEV, absence seizure and behavior change can improve the safety of LEV

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modification, in this paper, there is the discussion about the role of the dopamine in the absence seizure, LEV pharmocology and behavior change.

2. Pathology of absence seizure

The absence seizure is characterized by paroxysmal loss of consciousness and bilaterally synchronous spike like-wave discharge [8]. Numerous tons of studies have found that the absence seizure is generated from abnormal network oscillation [1]. During the absence seizure, researchers found some areas of the brain had different EEG recordings compared with normal people. According to Blumenfeld, the bilateral spike-wave is produced by maximal amplitude in the anterior region and thalamic nuclei are highly involved, they are not found in the occipital cortex and thalamic lateral geniculate nuclei which connect the with occipital cortex [1].

Degeneration of the nigrostriatal dopaminergic pathway lead the decrease of the dopamine level in the thalamus. The nigrostriatal pathway projects dopaminergic neurons from the subtantia nigra to the striatum and other brain region which involve in the motor control and cognitive function [7]. Absence seizures are typically generated within the cortico-thalamo-cortical network [7]. The basal ganglia, including the nigrostriatal pathway, modulate this network's activity. Disruptions in dopaminergic signaling within this pathway can lead to altered network dynamics, contributing to the generation and prolongation of SWDs [7].

The thalamic neurons are involved in consciousness generation [9]. The thalamic neurons can inversely convert the oscillatory model to a tonic firing mode [9]. This change is associated with consciousness change. During the signal transmission from the environment to the cortex, the thalamic neurons transmit signals in a tonic fire-model. On the other hand, when those neurons produce an oscillatory mode, the threshold of the excitatory postsynaptic potential (EPSP) in the thalamus is raised, signal transmission is blocked and as a result the consciousness is altered [9].

The oscillatory neuron found in the nucleus reticularis thalami (NRT) and interacts with the GABAergic neuron, the NRT neuron detects the excitatory signal from the glutaminergic neuron from the axon coloateral of thalamocortical fibres [9]. This NRT neuron has the ability to shift between oscillatory and tonic firing modes to influence the flow of stimuli to the cortex from the external world to the thalamus. This process is driven by a low-threshold Ca^{2+} spike triggered by GABA-mediated late inhibitory postsynaptic potentials (IPSPs) [9].

In absence seizure patients, there is a developmental perturbation of the thalamocortical circulatory system or maldevelopment of the neurotransmitter system in the thalamus and cortex. This may result from the subtle developmental shift in the balance of N-methyl-D-aspartate (NMDA)-mediated excitation and GABA-mediated inhibition leading to thalamocortical oscillation and synchronous spike wave discharges (SWD). The SWDs are generated by an increase in firing of cortical neurons, which leads to a large synchronized increase in neuronal firing in the thalamocortical network [10]. Some research found that enhancing GABAergic inhibition contributes to the sybchronization of SWD, moreover, the benzodiazepines effectively inhibit the absence seizure by suppressing GABA-mediated inhibition in relay neurons and reducing SWD duration. Reduced dopaminergic activity leads to disinhibiton of thalamocortical leads to disinhibition of thalamocortical nerions. This disinhibition can enhance the excitatory inputs to the thalamus contributing to the maintenance of the rhythmic oscillation necessary for SWDs [7].

Glutamate mediates absence seizures through excitatory amino acid-mediated mechanisms, specifically involving recurrent excitation between thalamocortical and corticothalamic pathways that project excitatory axon collaterals to the NRT [9]. Experimental models of generalized absence seizures have shown that pharmacological manipulation of NMDA-mediated excitation can significantly impact spike-wave discharge (SWD) duration, with NMDA agonists or antagonists affecting SWD duration in various models [9]. Additionally, the regional distribution of NMDA receptor complex components and enhanced NMDA-mediated excitation in specific cortical layers have been linked to the pathogenesis of absence seizures [9].

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3. Levetiracetam introduction

3.1. Pharmacology of levetiracetam

Compared with other novel antiepileptic drugs, the LEV shows differences in its structure and mechanism of action. The LEV tends to bind to the synaptic vesicle protein SV2A, this protein has 12 transmembrane integral 90-KDa protein with widespread distribution in the brain, and it can regulate synaptic vesicle exocytosis which contains the cofactor (e.g. Ca^{2+} and ATP) of action potentials and neurotransmission release include dopamine [11]. LVE interaction with the LEV can inhibit the release of the neurotransmitter [12]. People found that when the SV2A gene is mutated in mice, there is a decrease of GABA release. In contrast when increasing the SV2A expression, there is a increase of GABA release. However, those experiments also found the SV2A expression changes do not impact the release of glutamate, which means GABAergic neuron and SV2A may have a close relationship and their own mechanism [13].

LEV also reduces the presynaptic glutamate release in the dentate gyrus of the hippocampus[14], which is involved in the seizure activity [15]. In detail, there are three types of voltage-gated calcium channels, including the L-, N- and P/Q voltage-gated calcium channel. They all mediate the Ca^{2+} transient in presynaptic nerve terminal and they can co-exist at different parts of the brain, but the LEV only interacts with the P/Q channel to decrease the glutamate release [14]. Besides, LEV can inhibit part of the N-type channel to impact the calcium signal in hippocampal neuron by making Ca^{2+} leak from endoplasmic reticulum which achieved by the blockage of ryanodine receptor. It also blocks the L-type Ca^{2+} channel to prevent the Ca^{2+} from entering [11]. Moreover, the LEV can inhibit the Ca^{2+}release by inhibiting the IP3 receptor in hippocampal neuron. This is achieved by exerting IP3 triggered Ca^{2+} store depletion, but it does not reduce the Ca^{2+} storage [13].

3.2. Adverse effects of levetiracetam

LVE has been reported to have adverse effects, which are divided into positive or enhanced cognition function and negative effects (inducing aggressive, hostile and violent behavior) [16]. For instance, Gomer et al. indicate that LEV can enhance attentional function [17], and Piazzzin et al. and Paola Canevini et al. refer to improvements in speech organized by the frontal lobe, which means the LEV can improve the function of this brain area [18-19]. Most importantly, compared with other antipsychotic drugs, such as topiramate, which would make frontal-lobe associated function worsen after treatment, the LEV has no such side-effects, which may be due to its good tolerability [17]. On the other hand, deactivation of temporal structure, which is mediated by LEV, is associated with enhancement of cognition performance [20]. Besides, low dose LEV can improve the spatial memory and executive function in Alzheimer disease patients [21], this improvement is associated with the increase activity of the medial temporal lobe [22]. According to Lin et al., disruption of fronto-parietal- medial temporal connections has been found in in Alzheimer Disease and other cognition dysfunction diseases [23]. This connection is associated with executive ability and episodic memory and this connection can be improved by LEV. The possible mechanism of this improvement may be that LEV mediates the GABA and glutamate release [23]. Koh et al. have found that LEV can enhance the memory ability in ketamine animal mode of schizophrenia which simulates the hyperactivity and memory problems in schizophrenia patients [22]. They tested LEV with another antipsychotic, risperidone. What they found is that LEV can dose-dependently improve the hippocamps-dependent memory even when there is another antipsychotic [22]. Based on all the above, LEV enhances cognition meanly through an increase in SV2A's inhibition function to reduce the frontoparietal- medial temporal connections excitatory ability.

However, there are some negative side effects. The systematic review said that the most common side effects were in the children, where hostility, nervousness and aggression are found [24]. The severity of these side effects does not appear to be related to the dose of the drug, but studies have shown that the dose of the drug is related to the severity of the side effects [25]. For example, Helmastaedter et al. found that researchers cannot predict the effect of the LVE based on the dose [16]. On the other hand, Helmastaedter et al. reported that people who have intelligent problems have poor seizure control under

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the LEV treatment and they also indicated that the psychotic effect of LEV was related to the success of seizure control [16]. Moreover, Helmastaedter et al. referred that the negative effects tend to be found in patients who have impulsive and aggressive personal traits [16]. Later, in 2012 they found that aggression-related genes which regulated the dopaminergic signal were related with aggressive behavior and LVE interrupt the dopaminergic signal which increased the risk of negative psychiatric effects [26].

4. Conclusion

According to the above description, absence seizure is related to abnormal neurotransmitter release in the thalamocortical circuit, which causes abnormal excitation of frontoparietal-medial temporal connections, affecting the function of these brain areas. The most obvious symptom is a loss of consciousness. The LVE enhances the cognition improvement mainly by interacting with the SV2A molecule in the thalamiccortex network to mediate the release of GABA and glutamate. The LVE may alter the behavior of the patient, interestingly, this behavior change is not related to the dose or any other factors, the behavior altered is dependent on the personal trial. In other words, it may be relative to different ploymorphism of dopaminergic related genes, for instance, altering gene variants of catechol-O-methyltransferase (COMT), monoamine oxidase (MAO) dopamine D2 receptor gene can change the behavior effect of the LVE [26]. This further reflects the importance of maintaining the dopamine level [26]. Furthermore, after LEV and SV2A binding, the difference in neurotransmitter release can lead to different consciousness and behavior. However, this paper have not found exactly mechanism of how LVE can modulate the dopamin level and there are not many reference shown a impact between gene polymorphism related to dopamine release and consciousness and behavior. Future research could focus on the relationship between common polymorphism and behavioral changes in LVE, this can help to improve the safety of LVE treatment in absence seizure.

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