Purkinje Cells and Epilepsy

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Abstract

The cerebellum is a structure composed of the cerebellar cortex and deep nuclei. In the cerebellar cortex, are located the Purkinje cells (PC) which exert inhibitory control over the deep nuclei by releasing GABA. The PC receive glutamate through the granular cells axons or through the climbing fibers. PC are larger susceptible to excitotoxicity than other cerebellar cells, the PC contain α-amino-3-hydroxy-5-methyl-4-isoxazolepropanionic acid receptor (AMPAR) and metabotropic receptors to glutamate which increase the excitotoxicity by excessive release of glutamate from the parallel fibers that would lead to PC death. Epileptic seizures have been widely associated with cerebellar pathologies. Moreover, it has been found a widespread loss of PC in postmortem brain tissues from epileptic patients. In the kindling model of epilepsy, the total cerebellotomy increases the duration of generalized seizures, probably by the absence of the GABAergic inhibition to the forebrain. Contrastingly, specific lesions of the glutamatergic cerebellar nuclei, where the PC exerts its inhibitory effects, decreases the duration of the electrographic seizures and diminished the behavioral activity associated with this model. Therefore, the objective of this review is to evaluate the involvement of PC in the epileptic activity.

INTRODUCTION

Cerebellar purkinje cells and epilepsy

The cerebellar cortex is a structure composed by five types of cells distributed in three layers; the external or molecular layer containing the basket cells, stellate cells [1], the dendritic arborization of the Purkinje cells (PC) and the parallel fibers; the medial or mono-layer containing the soma of the PC; and the internal or granular layer containing the granular cells their axons conform the parallel fibers [2]. Different studies show that manipulation of these structures in epilepsy models can suppress or increase the duration of epileptic seizures, the intercommunication between these layers is a circuit that can regulate the levels of glutamatergic output to the brain, which has its main excitatory or inhibitory regulation through PC. Degeneration of the PC in patients with generalized tonic clonic seizures was observed through the magnetic resonance [3] also in postmortem brain tissue of patients with status epilepticus prolonged [4], this information confirmed the loss PC in the epileptic activity. In Mongolian gerbil’s strains, susceptible to spontaneous seizures, PC are reduced after seizures, supporting the hypothesis that neuron loss is a possible consequence of generalized seizures [5]. Whatever the case, severe epilepsy revealed significant decreases in PC and their dendrites [6].

The loss of PC in the epileptic phenomenon is clear, although the mechanisms by which this reduction occurs in the population of the PC is not fully elucidated. However, experimental evidences show mechanisms that could lead to death of these cells. It is known that the PC are susceptible to damage due to excitotoxicity [7], for example, the intraventricular injections of glutamate or aspartate produce seizures, degeneration and loss of the PC [8]. In generalized seizure, high levels of intracellular Ca²⁺ triggered a sequence of intracellular events that lead to cell death in rats [9]. Similar events are reported after the electrical stimulation in parallel fibers and epileptic brain slices, which increase the intracellular Ca²⁺ concentration in the PC that could conduce to death [10-12].

The slices comparison the tottering mice (a mouse model of absence epilepsy) and the wild-type mice show differences in the glutamatergic transmission between parallel fibers and PC, in the glutamate release of the parallel fiber in the wild type is through of the P/Q-channels activation, in contrast the parallel fiber tottering mice is controlled by class B Ca²⁺ channels (N type) [13]. The loss of P/Q type channels in PC of mice leads to aberrant phenotypes as ataxia, dyskinesia and epilepsy absence, these phenotypes are explained through the synaptic transmission of parallel fiber with PC which is reduced during low frequency stimulation in these mice, suggesting that the intrinsic impaired production of PC is a pathogenetic factor sufficient for initiation of the disease [14].

The ducky mutant mouse with a truncation mutation in gene encoding delta-2 alpha-2 voltage dependent Ca²⁺ channel accessory subunit (CACNA2D2) strongly expressed in the PC that produce absence epilepsy, cerebellar ataxia and abnormalities in the PC dendritic tree [15]. Other mouse with a mutation in the
Ca\textsuperscript{2+} channel CACNA1A manifested ataxia, seizures and cerebellar atrophy shows in particular, a gradual degeneration of the PC [16]. Both phenotypes show the cerebellum reduced in size, persistence of the PC with immature and grossly abnormal morphology, including multiple primary dendrites and reduction in the size of the PC dendritic tree [15,16].

Other mechanism of damage of PC in epilepsy processes were explored. In the cerebellum of gerbils with epileptic seizures, the level increase of Ca\textsuperscript{2+} causes dephosphorization and intracellular degradation of the neurofilament (NF) in the PC [17] also, independent mechanisms Ca\textsuperscript{2+} has been explored, [18] demonstrated that the loss of Na\textsuperscript{+} currents produce degeneration in the PC. So far we have reviewed the participation Ca\textsuperscript{2+} and Na\textsuperscript{+} channel, but the involvement of K\textsuperscript{+} in the PC in epilepsy has also been tested with the Christianson syndrome (CS) a neurological disorder caused by mutations in the slc9a6 of K\textsuperscript{+} channel gene and characterized by symptoms including epilepsy, ataxia, hyperkinesia and microcephaly [19]. Male mice with mutation in the slc9a6 gene develop degeneration in PC [20].

Stargazer mouse characterized by ataxia and seizures, show reduction of the synaptic function in PC. Stargazin is a protein mutated in these mice that promotes the expression and activation of neuronal AMPA receptors (AMPARs). These findings suggest that altering the AMPARs can contribute to PC alteration and phenotypes of absence seizures and ataxia [21]. In the genetically epilepsy-prone rats (GEPR) was demonstrated the alteration in the GABA transmission in the PC, using intracellular recordings was found the reduction of responses to receptor agonists GABA\textsubscript{A} compared to non GEPR strain rats [22].

So far we have reviewed the alterations or death of the PC in the tonic clonic epilepsy or the status epilepticus, another neurologic disease that causes epileptic disorders is the tuberous sclerosis complex (TSC), which is caused by a mutation that inactive the genes coding for hamartin (TSC1) and Tuberin (TSC2) proteins. The TSC2 loss causesa progressive increase in the cell size endoplasmic reticulum size, oxidative stress and apoptosis of the PC associating this with motor deficit [23].

In this review, we briefly examined some of the studies in the most significant advances in the areas of genetics and electrophysiology and cell to elucidate mechanisms the damage in the PC and participation of this in epileptic activity. While it is unclear the role of CP in epilepsy, biochemical, molecular and anatomical studies involve the electrophoretic activity of this cell group in the pathophysiology of this disease. Optogenetical studies show that regulation of the stimulation of CP inhibits hippocampal seizures induced by kainic acid [24], similarly, our group recently showed that lesions of the cerebellar nuclei receiving directly afferent of the CP, decrease the time duration of epileptic seizures, by a mechanism that involves increased GABA in the red nucleus [25]. These findings open a line of research involving the CP transmission cerebellar nuclei and their neuroanatomical outputs (red nucleus, thalamus, sensory motor cortex) to control seizures in epilepsy.

REFERENCES


