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REVIEW

Cortical Neuronal Types and Epilepsy

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Abstract

Epilepsy has been defined as an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.

Although the district pathophysiology of epileptic discharge has not clearly clarified, seizures require three conditions: (1) a population of pathologically excitable neurons; (2) an increase in excitatory, mainly glutaminergic, activity through recurrent connections in order to spread the discharge; and (3) a reduction in the activity of the normally inhibitory GABAergic projections.

In the present study we briefly present the neuronal types of the cerebral cortex, and their potential role in epilepsy.

Key words*:* cortical, neuronal, epilepsy

Introduction

Epilepsy has been defined as an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition [1]. Epilepsy is classified by etiology in 1. Idiopathic which is defined as an epilepsy of predominately genetic or presumed

genetic origin and in which there is no gross neuroanatomic or neuropathologic abnormality, 2. Symptomatic, which is defined as an epilepsy of an acquired or genetic cause associated with gross anatomic or pathologic abnormalities, and/or clinical features indicative of underlying disease or condition, 3. Provoked, defined as an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuroanatomic or neuropathologic changes. Provoked epilepsies could also have a genetic basis, and 4. Cryptogenic epilepsy, defined as an epilepsy of presumed symptomatic nature in which the cause has not been identified. Cryptogenic epilepsies account for at least 40% of adult onset epilepsies [2]. Furthermore epilepsies are classified according to their clinical features to partial or focal, with topographic or lobar localization and generalized which include generalized tonic-clonic seizures, tonic seizures, clonic seizures, atonic seizures, myoclonic epilepsies and absence seizures [3].

Although the district pathophysiology of epileptic discharge has not clearly clarified, seizures require three conditions: (1) a population of pathologically excitable neurons; (2) an increase in excitatory, mainly glutaminergic, activity through recurrent connections in order to spread the discharge; and (3) a reduction in the activity of the normally inhibitory GABAergic projections. [4, 5].

Numerous recent studies showed different and even crucial roles for excitatory and inhibitory neuronal types of the cerebral cortex in the generation and transmission of epileptic discharge.

In the present review we present the neuronal types of the human neocortex and their potential role in epilepsy.

Neuronal types of human neocortex

Human cerebral cortex is divided in six layers, which contain a characteristic distribution of neuronal types. From pial surface to white matter cortical layers are:

1. Layer I, the molecular layer, contain few neurons, namely Retzius-Cajal cells and some scattered spiny stellate cells, as well as horizontally oriented axons. Layer I across the cerebral cortex mantle receives substantial input from M-type thalamus cells [6].
2. Layer II, the external granular layer, contain small sized pyramidal cells and stellate cells.
3. Layer III, the external pyramidal layer, contains predominantly small and medium-sized pyramidal neurons, as well as non-pyramidal cells with ventrically oriented intracortical axons.
4. Layer IV, the internal granular layer, contains different types of stellate and pyramidal cells. Layer IV is the main target of thalamocortical afferents from type C neurons, and intra-hemispheric afferents.

5. Layer V, the internal pyramidal layer, contains large pyramidal neurons which give rise to efferent axons to subcortical structures.
6. Layer VI, the multiform layer, contains few large pyramidal neurons and many small spindle-like, ovoid or polyhedric neurons. Efferent fibers from this layer target thalamus, establishing a very precise reciprocal interconnection where layer VI neurons connect with thalamus neurons that provide input to the same cortical column [7].

Human cerebral neocortex consists of numerous neuronal types, each exhibiting specific structural and functional features. These neuronal types are classified in two classes of neurons, the excitatory and the inhibitory ones. The first neuronal class contains pyramidal and stellate spiny neurons which use glutamate or aspartate as neurotransmitter and typically send their axons to distant cortical and subcortical targets. The inhibitory class of neurons contains local-circuit interneurons, whose axonal arborization is restricted to the neocortex and use GABA as neurotransmitter. GABAergic neurons represent about 20-30% of neocortical neurons [8].

Pyramidal neurons

Pyramidal neurons have pyramidal cell somata sized from 15 to 45μm and an apical dendrite rising from the top and orienting to the pial surface. From the basis of cell soma rise 2-5 primary basal dendrites which ramify to secondary and tertiary branches and forma dense dendritic field. The basal dendritic branches are connected to basal dendrites of adjacent pyramidal cells and subserve horizontal transmission. Pyramidal cells are found in all except from the molecular, layers of the neocortex and are projection neurons while their axon leaves the cortex and targets other cortical (for pyramidal cells of layer III) and subcortical areas (for pyramidal cells of layers V and VI) [8].

Inhibitory neurons

The functions of cortical inhibitory neurons are accomplished through remarkable diversity of subgroups distinguished by somatodendritic morphology functional properties and connectivity. Inhibitory neuronal types are [9]:

a. ***Basket cells.*** They are named by the basket-like appearance of their preterminal axonal segments around the somata of pyramidal neurons. Basket cells are divided into three distinct subclasses: large, small and nest basket cells and represent about 50% of inhibitory neocortical neurons. Their axonal boutons target somata and proximal dendrites of pyramidal neurons and other interneurons. The majority of basket cells belong to the fast-spiking cells and they ensure perisomatic inhibition which has a regulatory effect on synchronization and oscillatory activity of large

population of pyramidal cells. Large basket cells give rise to vertically and horizontally oriented axonal collaterals and are the primary source of horizontal inhibition across cortical columns, within the layer that contains their somata.

b. ***Chandelier cells.*** They represent a type of aspiny interneurons with radially oriented dendrites and oval, multipolar or bi-tufted cell soma. Their axons exhibit extensive branching of its preterminal segments, which form short vertically oriented rows of boutons resembling rows of candles in a chandelier. The terminal boutons of their axons have been shown to innervate only the axon initial segments of pyramidal cells forming symmetrical synapses. Chandelier cells are considered to be the most powerful cortical inhibitory system, since they are distributed along the majority of cortical layers and the initial segment of the axon is a strategical region where the action potential is generated. Recently it was demonstrated that Chandelier cells target the distal region of the axon initial segment containing voltage-gated Kv1.2 channels.
c. ***Martinotti cells.*** They are found in layers II-V and less frequently in layer VI. Martinotti cells represent about 15% of interneuronal population and possess ovoid or spindle like somata. Their dendrites are vertically oriented and extend to the infragranular layers and their axons project towards layer I, where the form a cluster of collaterals spreading horizontally. Martinotti cells receive inputs from several layers within the diameter of a cortical column and are functionally low threshold regularly spiking neurons.
d. ***Double-bouquet cells.*** Double-bouquet cells are found in layers II-V and exhibit a bi-tufted dendritic morphology. Their axons are descending, vertically oriented and coupled into fascicles resembling horse tail. Double-bouquet cells innervate dendritic spines and shafts and participate in interlayer and intracolumnar inhibition.
e. ***Bipolar cells.*** They are small cells with ovoid or spindle like somata and bipolar or bi-tufted dendrites that extend towards layer I and layer VI. Their axons form a narrow band that crosses all layers and form axo-dendritic synapses with pyramidal cells.
f. ***Bi-tufted cells.*** Bi-tufted cells have ovoid somata and bi-tufted dendritic fields. Their axons are distributed among neighboring layers and target the dendrites of pyramidal cells.

Pyramidal cells and Epilepsy

Neuropathological and neuromorphology studies on the pyramidal cells in epileptogenic regions of cerebral cortex, revealed significant dendritic and spinal alterations. Scheibel et al in a Golgi study of pyramidal cells in cases of Temporal

lobe epilepsy described severe loss of dendritic branches and spines, as well as focal nodules along dendritic shafts and axons [10]. Moreover Jiang et al in a rat model of early-onset epilepsy noticed significant loss of dendritic spines and morphological alterations of dendritic trees, regarding dendritic diameter and orientation [11]. They suggested that the morphological abnormalities of pyramidal neurons, could significantly change the electrical signalling within dendrites and may condribute importantly to seizures and behavioural sequlae of early-onset epilepsy [11].

1Pyramidal cells constitute the main output system of the neocortex, projecting to various subcortical brain areas including the striatum, brainstem nuclei and spinal cord [12, 13]. The distal portion of their apical dendrite in layer 1 is targeted by thalamic afferent input [14] and by afferents from other cortical areas [15, 16]. The overexcitation and afterdischarge generation, driven by glutaminergic transmission which is mediated through the AMPA-type and NMDA-type receptors of pyramidal cells, resulting in excess activation of their targets, plays a crucial role in epilepsy [17]. Prolonged regeneration of calcium spikes on dendrites results on high-frequency bursting and oscillations of pyramidal cells. Synchronization and oscillatory activity of pyramidal neurons, and more specific fast oscillations have been shown to participate in epileptic discharge, while GABA A mediated synapses forming with axon terminals of large fast-spiking basket cells are involved in the inhibition of epileptic discharge transmission [17].

The Role of Chandelier, Basket cells and Martinotti cells in Epilepsy

Neuropathological studies of epileptogenic foci have revealed severe neuronal loss, mainly of GABAergic neurons and more specific of Chandelier and Basket cells, as well as extensive gliosis [18, 19]. Williams et al described significant and selective loss of symmetrical inhibitory synapses on the distal regions of the initial segments of axons of pyramidal cells in a patient suffering from neuronal ceroid lipofuscinosis with generalized slow and paroxysmal findings on EEG. They concluded that this selective loss of inhibitory synapses was the main cause for the paroxysmal activity on EEG [20].

Produttur et al using cellular recording methods and NEURON simulation environment [21], showed that fast-spiking basket cells and specifically the large basket cells plays a substantial role in the transmission of epileptic discharge, while they are responsible for the horizontal inhibition and the control of synchronization and oscillatory activity of large populations of pyramidal cells [22]. Lachance-Touchette et al have recently described the effect of certain mutations of GABA A receptors regulating genes on the morphology of Basket cells and on the spines and synapses that they form with the pyramidal cells [23].

Moreover De Felipe et al using immunohistochemistry and antibodies against paralbumin that target electively GABAergic cells of the neocortex, noticed severe loss of Chandelier and Basket cells on brains from patients suffered by different types of epilepsy corroborating the crucial role of these cell types in epileptic activity [24].

Silberber and Markram showed that the Martinotti cells regulate a disynaptic inhibitory feedback pathway between layer 5 pyramidal neurons and are capable of preventing the prolonged regeneration of calcium spikes and high-frequency bursting of pyramidal cells [25].

The question that rises then, regards the role the rest types of GABAergic cells in epilepsy and the unique role of Chandelier cells and secondarily Basket cells. Every pyramidal cell form hundreds of inhibitory synapses with numerous GABAergic cells, however the strategic position of the synapses of Chandelier cells and their relatively small number in comparison to other GABAergic cells, render them of unique and substantial role in the control of epileptic activity [26]. Fujiwara-Tsukamoto et al demonstrated that the synapses of Chandelier and Basket cells on Pyramidal cells are of exceptional significance on the controls of epileptogenic and epileptic activity [17]. Although the selective loss of Chandelier and Basket cells and their synapses deranges the balance between excitatory and inhibitory activity of the cerebral cortex, it is wide accepted that more factors should contribute for the majority of epileptic seizures [27, 28].

Many types of epilepsy which had been considered to be of the Idiopathic category are now correlated to certain molecular disorders [29]. Nevertheless the majority of epilepsies with adult onset remains of unknown etiology [3]. Chandelier and Basket cells disorders could be the main etiologic factor in some of these cases. Furthermore, GABAergic cells' dysfunction is known to play crucial roles even in cases of epilepsy with certain organic background. Indisputably the role of GABArgic activity in the control of epilepsy can be recognized by the beneficial role of antiepileptic agents [29].

Neuronal morphology and Epilepsy

Dendrites of pyramidal cells are morphologically complex and receive tens of thousands of excitatory synaptic contacts. Although, dendrites were thought to passive [30], more recent evidence has shown that their plasma membrane bears voltage-dependent channels [31-33]. Results suggest channel distribution is far from homogeneous, and subsets of dendritic branches likely have different physiological properties.

Morphological alterations of dendritic arbors are likely to have important consequences on neuronal firing patterns and functioning. Indeed, dendrites appear to be anatomically plastic [34-36] and more specific the distal and terminal branches are the most plastic components [37]. Dendritic abnormalities have also

been described in human diseases [38-40], particularly in focal epilepsy. Studies have consistently reported reductions in dendritic spine density on pyramidal cells from epileptic patients. In addition, a loss of dendritic branches and varicose swellings are commonly observed on the remaining dendrites [41-44]. Studies of animal models of chronic focal epilepsy [45, 46] have reported similar dendritic changes.

Specific mutations of GABA A receptors which are related to epilepsy, have been shown to play a key role during brain development, influencing all developmental steps from neurogenesis to establishment of neuronal connectivity and resulting in certain morphological alterations of dendritic spines of pyramidal neurons [47, 48]. Recent studies demonstrated that GABA regulates axonal branching and synapse formation of cortical basket cells, through activation of GABA A and GABA B receptors [49, 50].

Conclusions

Both excitatory and inhibitory cortical schemes are involved in epilepsy. Although certain morphological alterations of pyramidal neurons and changes in their firing patterns and functionality are found in many cases, the most recent and complete model of epilepsy requires dysfunction and/or morphological alterations of inhibitory interneurons, and mainly Basket cells and Chandelier cells, while Martinotti cells are also concerned.

Despite the fact that the role of specific neuronal types is of exceptional significance in epilepsy, if the pathological alterations described by relevant studies are the cause of the result of epileptic activity remains unanswered for the majority of cases.

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