Introduction

It has long been known that epilepsy is a common chronic brain disorder. The factors underlying epilepsy are multifaceted, but recent research suggests that the brain’s neural circuits, which play a key role in controlling the balance between epileptic and antiepileptic factors, may lie at the heart of epilepsy. This article provides a comprehensive review of the neural mechanisms and potential treatment of intractable epilepsy from experimental and clinical studies.

Epilepsy and neural inflammatory responses

Increasing evidence shows that neural inflammatory responses in the epileptic focus contribute to the pathophysiology of seizure-induced brain damage. It is well known that there is a direct relationship between epileptic activity and CNS inflammation [1, 2], which is characterized by accumulation, activation, and proliferation of microglia and astrocytes. Early studies of intractable epilepsy concentrated on astrocyte activation and regional changes, but recent work has emphasized its microglial function [3, 4]. Najjar et al reported that microglial activation and proliferation were prevalent in resected human epilepsy tissue from a consecutive series of 319 surgically treated epilepsy cases, suggesting that microglia may initiate a cycle of inflammation-induced seizures and seizure-induced inflammation, and microglia-driven epilepsy may be a primary pathogenic process [5]. Studies from Mayo clinic health system support the pathogenic role of neuroinflammation in medically intractable epilepsy [6]. Further studies are needed to clarify the effects of neural inflammatory responses on intractable epilepsy and seizure-induced brain damage.

Epilepsy and melanocortin circuits in brain

A very close relationship between astrocyte activation and medically intractable epilepsy has attracted much scientific interest in the past few decades. The central melanocortin signaling is a key regulator of energy metabolism and glucose metabolism, and this effect is mainly mediated by the melanocortinergic receptor (MCR) expressed in the brain [7, 8]. A number of studies have verified that MC4R in the central nervous system plays an important role.
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Role in regulating the release of insulin via the activity of sympathetic neurons [9]. Otherwise, being the predominant MCR subtype in the brain, the MC4R is demonstrated to specifically express in astrocytes [10-12]. Because of its roles in controlling between astrocyte activity and energy balance in many brain regions, MC4R on astrocytes has been a focus of interest [10].

It was known that stimulation of the subthalamic nucleus was proposed as a therapeutic approach to alleviate refractory epilepsy [13-16]. Of interest, Accumulating evidence from functional imaging and clinical neurophysiology have demonstrated that therapeutic mechanisms of subthalamic nucleus stimulation are closely related to the changes in cerebral glucose metabolism and blood flow [17, 18]. The understanding of neuroanatomical connections in subthalamic nucleus is very important for studying the possible mechanism of subthalamic nucleus (STN) stimulation to refractory epilepsy. We had characterized different neuro-
nal populations of the subthalamic nucleus neurons in adult transgenic mouse line expressing green fluorescent protein (GFP) under the control of the MC4R promoter [19]. We observed the expression of glial fibrillary acidic protein (GFAP)-immunoreactive cells in the MC4R-GFP reporter mouse by using fluorescence immunohistochemical detection, and found that GFAP-positive neurons were mainly labeled in the dorsal STN and sparsely distributed in the ventral STN, suggesting the dorsal STN is the principal subregion to participate in the regulation of astrocytic activity. Supporting the hypothesis of STN activation is the observation that STN stimulation induced different changes of the local cerebral blood flow (rCBF) responses as assessed by $^{15}$O H$_2$O positron emission tomography during dorsal STN versus ventral STN stimulation by astrocyte activation, suggesting STN stimulation acts through distinct neuronal pathways dependent on stimulation location [20]. Meanwhile, we also found that MC4R-GFP was mostly co-localized with GFAP-positive cells in the dorsal STN but seldom coexpressed in the ventral STN. Supporting the hypothesis of STN activation is the observation that STN stimulation increased the regional cerebral metabolic rate of glucose (rCMRGlc) in the middle frontal gyrus and the right anterior or lobe of the cerebellum by employing FDG-PET study [21]. These results showed the melanocortinergic receptor mechanism of the modulation of astrocyte activity in the subregions of subthalamic nucleus.

**Epilepsy, rapid eye movement sleep and pedunculopontine tegmental nucleus**

Many lines of evidence show that susceptibility to epilepsy is increased during nonrapid eye movement (NREM, slow-wave) sleep whereas rapid eye movement (REM) sleep suppresses seizure occurrence [22-25]. Shouse et al reported that the neural generators of different sleep components can provoke seizure discharge propagation during NREM sleep, and can suppress it during REM sleep [26], suggesting that REM sleep may be a natural antiepileptogenic system in the body during the wake-sleep cycle. Therefore, intervening REM sleep may exert anti-epileptogenic influence.

The pedunculopontine tegmental nucleus (PPTg), which is in the lower midbrain, is considered a part of the reticular activating system [27, 28], and exhibits a wide heterogeneity in terms of the neurochemical properties (cholinergic, catecholaminergic, serotonergic, glutamatergic-containing neurons, and GABAergic interneurons) and connectivity (afferent and efferent connections to the thalamus, cerebrum and spinal cord) [29-33]. Report from Hayashi et al showed that acetylcholinergic neurons in the PPTg were involved in mental development, and disruption of neuronal nicotinic acetylcholine receptors led to epilepsy [34]. It is demonstrated that stimulation of unilateral PPTg can selectively promote nocturnal REM sleep [35-38], and PPTg has been recently highlighted as an effective target of deep brain stimulation for seizure treatment in patients with intractable epilepsy who are unsuitable candidates for epilepsy brain surgery [39, 40]. Otherwise, data from Schwartz et al showed that cholinergic agonist microinjection to the pontine produced polygraphic features of REM sleep [25]. So, the activation of specific pontine focus by nerve stimulation may induce REM-like state and suppress seizure occurrence.

Transneuronal tracing with neurotropic pseudorabies viruses (PRV) has greatly advanced our understanding of multisynaptic circuits between the PPTg and peripheral tissue. It has been shown previously that there is strong cholinergic innervation from PPTg to the thalamus and pons, which is involved in the generation of muscle tone and REM sleep [34, 39]. These neural bases may partly explain many clinical symptoms that there exist visual, auditory and gastrointestinal complaints in patients with intractable epilepsy (Figure 1). Knowledge on the neural bases of minor gastrointestinal symptoms may help to describe those systems associated with the gastrointestinal phenomena in epilepsy. The past two decades have witnessed an explosion in the recognition that the CNS cell groups that project to the gastric sympathetic preganglionic neurons were identified by the viral retrograde transneuronal labeling method [41-43]. Card et al used synapse-dependent retrograde transneuronal transport of pseudorabies virus (PRV) to trace autonomic emotional motor circuit development from the stomach wall to CNS [44]. Banihashemi et al also reported that repeated brief postnatal maternal separation enhanced hypothalamic gastric autonomic circuits in juvenile rats [41]. Gao et al used PRV-152 expressed EGFP to inject into the stomach wall, and found that
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neurons expressed EGFP 60-72 h subsequent to PRV-152 inoculation of vagal terminals in the stomach wall were targeted in transverse brainstem slices [42]. In our experiment, PRV-614 was injected into the stomach wall, and after 5 days survival, the animals were perfused and their brains processed for immunohistochemical detection of PRV-614 [31, 45, 46]. We found that neurons of the STN and PPTg were retrogradely labeled with PRV-614 (Figure 1B), suggesting that neurons in STN and PPTg are tightly linked to the regulation of gastric functions.

Potential treatment of epilepsy

Collectively, the neural mechanisms play an important role in controlling the pathogenic development of pharmacologically resistant epilepsy. The past three decades have witnessed an explosion in the recognition of the safety and effectiveness of vagus nerve, STN and responsive cortical stimulation as an adjunctive therapy for partial onset seizures in adults with medically refractory epilepsy [47-49]. Further studies should be undertaken to elucidate the nature of vagus nerve, STN and responsive cortical stimulation so that we may more effectively apply these new preventive and symptomatic therapies to the patient suffering from medically refractory seizures and its complications.

Disclosure of conflict of interest

None to declare.

Address correspondence to: Dr. Hong-Bing Xiang, Department of Anesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, PR China. E-mail: xhbtj2004@163.com

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