Therapeutic mechanism of subthalamic nucleus stimulation for refractory epilepsy involved in melanocortin-4 receptor signaling

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Despite there exist obvious metabolic changes within brain after subthalamic nucleus stimulation for refractory epilepsy, our understanding about the neuroanatomical and neurochemical mechanisms of subthalamic nucleus stimulation is still limited. Melanocortin receptor subtype 4 (MC4R) has been shown to mediate melanocortin effects on cerebral glucose metabolism, and, recently, to modulate astrocyte functions. This review described that subthalamic nucleus stimulation involved in the changes in regional cerebral glucose metabolism, and MC4R signaling in the brain. We discussed the possible therapeutic mechanism of subthalamic nucleus stimulation for refractory epilepsy. It is highlighted that improvement of epileptic signs associated with subthalamic nucleus stimulation might involve in melanocortin-4 receptor signaling on neurons and astrocytes, not only in the target, but also in surrounding and remote connecting regions.


Introduction

Brain stimulation for patients with refractory epilepsy has always been challenging. This is an invasive procedure, and the high cost has hampered its more extensive application. The mechanisms accounting for this effect are unknown but, from accumulated experience with the use of brain stimulation in the management of refractory epilepsy, it is known that therapeutic mechanisms most probably activated by brain stimulation are the changes in regional cerebral glucose metabolism [1, 2]. We suggest that the therapeutic effect of brain stimulation results from direct activation of melanocortinergic pathways controlling changes in cerebral glucose metabolism. Subthalamic nucleus stimulation has recently been proposed as a therapeutic approach to alleviate refractory epilepsy [3-6]. On the basis of the striking changes in cerebral glucose metabolism induced by brain stimulation [7,8], we propose that therapeutic mechanism of subthalamic nucleus stimulation for refractory epilepsy may involve in melanocortin-4 receptor (MC4R) signaling [9].

Our research data about subthalamic nucleus

The subthalamic nucleus (STN), a small lens-shaped nucleus in the brain, is located ventral to the thalamus. It is also dorsal to the substantia nigra and medial to the internal capsule. In terms of anatomy, it is the major part of subthalamus. From a functional point of view, STN is part of the basal ganglia system, and the excitatory STN and the inhibitory external globus pallidus (GPe) play a
particularly important role in the regulation of substantia nigra pars reticulata (SNr) activity\textsuperscript{[10]}. Evidence derived mainly from clinicopathological studies had supported that subthalamic nucleus of the basal ganglia played an important role in motor control\textsuperscript{[11-14]}. However, there are few studies in intact subjects that have tested the therapeutic mechanisms activated by STN stimulation, except a functional neuroimaging study recently conducted in humans\textsuperscript{[7]}

It was a strikingly attractive that different neuronal populations present in the subthalamic nucleus neurons, e.g., glutamatergic, GABAergic, and dopaminergic neurons\textsuperscript{[15-17]}. The understanding of neuroanatomical sympathetic circuitry and neuronal connections in the subthalamic nucleus is important for studying the possible mechanism of subthalamic nucleus stimulation. We had characterized the projection from the kidney to subthalamic nucleus in adult transgenic mouse line expressing green fluorescent protein (GFP) under the control of the MC4R promoter by using retrograde transynaptic tracing techniques of pseudorabies virus (PRV)-614\textsuperscript{[18]}. We found that neurons expressing MC4R-GFP were distributed in the subthalamic nucleus, which were in line with a previous immunohistochemical study showing that the subthalamic nucleus exhibited moderate levels of GFP immunoreactivity using a mouse line in which GFP is expressed under control of MC4R gene promoter\textsuperscript{[19]}. Our results also showed that injections of PRV-614 into the kidney resulted in retrograde infection of neurons in the subthalamic nucleus, and PRV-614/MC4R-GFP dual labeled neurons were detected in the subthalamic nucleus. Because central regulation of sympathetic activity is a major component of melanocortinergic action\textsuperscript{[19-21]}, our data suggest that MC4R signaling in the subthalamic nucleus may involve in the sympathetic regulation.

It is well known that astrocytes play an important role in the regulation of neuronal activity in the subthalamic nucleus\textsuperscript{[22-23]}. Glial fibrillar acidic protein (GFAP) is a marker for astrocytes or astrocyte activity. We investigated GFAP expression in the subthalamic nucleus by fluorescence immunohistochemical detection. In addition, using a line of mice expressing green fluorescent protein (GFP) under the control of the MC4R promoter, we found double-labeled MC4R-GFP/GFAP neurons were detected in the subthalamic nucleus, suggesting that astrocytes in the subthalamic nucleus are tightly linked to MC4R signaling.

**Epilepsy, melanocortin-4 receptor, glucose metabolism and subthalamic nucleus stimulation**

It had been reported that ACTH that ameliorates infantile spasms, a severe epileptic encephalopathy of infancy, might act through activating the central MC4R to suppress excessive production of corticotrophin-releasing hormone\textsuperscript{[24]}, suggesting that there is a close link between MC4R signaling and pathological mechanism of epilepsy.

Using [18F]-fluoro-deoxyglucose (FDG)-positron emission tomography (PET) study, Hiller et al\textsuperscript{[25]} reported that the resting regional cerebral metabolic rate of glucose (rCMRglc) increased in the posterior cerebellar cortex with STN stimulation but decreased in the anterior cerebellar cortex, possibly related to relief of seizure. Batisse-Lignier et al\textsuperscript{[7]} had reported that endogenous glucose production (EGP) and whole-body glucose disposal rates (GDRs) were higher in Stim-OFF conditions than in the control group by assessing in the postabsorptive state during a primed continuous iv infusion of D-[6,6-(2)H]glucose for 5 hours in 8 STN-DBS-treated patients with PD, without (Stim-OFF) and during STN stimulation (Stim-ON) treatment. Nagaoka et al\textsuperscript{[28]} found that STN-DBS increased the regional cerebral metabolic rate of glucose (rCMRGlC) in the posterior part of the right middle frontal gyrus, which corresponded to the premotor area, and the right anterior lobe of the cerebellum by employing FDG-PET study, suggesting STN stimulation either activates the premotor area or normalizes the deactivation of the premotor area. Troxt et al\textsuperscript{[27]} found that STN stimulation reduced glucose utilization (ON < OFF) in a cluster of voxels within the rostral pons and midbrain, and associated with ipsilateral decrements in the primary motor cortex, supplementary motor area, and in the cerebellar vermis. In addition, Asanuma et al\textsuperscript{[28]} also described that rCMRglc in cerebellar vermis decreased by FDG-PET study. These findings strongly suggested that switching on STN stimulation led to a change in local glucose metabolism.

The central melanocortin signaling plays an important role in regulating appetite, body weight homeostasis and energy expenditure\textsuperscript{[29]}, and these effects are mediated mainly via activation of melanocortinergic receptors expressed in the brain, which is central to the control of food intake\textsuperscript{[30]}. A number of studies have verified that MC4R in the central nervous system are key regulators of energy metabolism and glucose metabolism, and have also been suggested to regulate the release of insulin via the activity of sympathetic neurons\textsuperscript{[31]}. MC4R is a member of the seven membrane-spanning G protein coupled superfamily receptors and belongs to the subfamily of melanocortinergic receptors\textsuperscript{[32]}. MC4R was
found to be expressed in a number of brain regions, including hippocampus, amygdala, subthalamic nucleus, hypothalamus, nucleus tractus solitarius and the dorsal horn of the spinal cord [19, 33, 34]. Evidence from clinical adult populations suggests that the coding mutations in the MC4R are the common genetic causes of severe human obesity [35, 36], and MC4R mutations can cause functional alteration of the activation of MC4R by affecting ligand binding affinity, and impact upon the regulation of energy homeostasis. It is speculated that STN stimulation- induced the changes of glucose metabolism are tightly linked to MC4R in CNS.

**Epilepsy, astrocytes, melanocortin-4 receptor and subthalamic nucleus stimulation**

Accumulating experimental reports suggest that astrocytes, the major glial cell type of the central nervous system (CNS), are viewed as crucial components of neural networks, synaptic transmission, and behavior by releasing chemical transmitters in a process termed gliotransmission [37]. Functions of astrocytes had been demonstrated to be dysfunctional in various neurological disorders (such as Parkinson's disease, epilepsy, etc.) accompanied by astrocytic hypertrophy, an increase in astrocytic processes and an upregulation of the synthesis of GFAP. Reactive astrocytes/astrogliosis are known to play a major role in the regulation of the immune/inflammatory response in several human CNS diseases [38]. Emerging evidence showed a critical role of astrocytes in epilepsy. It was believed that astrocytes form a significant constituent of seizure foci in the human brain, and the functions of the astrocyte vascular interface may be more critical to the processes involved in epileptogenesis [39-41].

Several lines of evidence confirmed that astrocytes modulated neuronal activity but their role depends on the brain structure concerned. As an important glutamatergic nucleus, STN occupies an active position in the functional architecture of the basal ganglia network [42]. An increasing body of evidence obtained the last few years has established that high-frequency stimulation of the STN could inactivate STN neurons or activate GPe neurons [43]. This normalization might reduce the hyperactivity of STN-GPe-SNr loops [44]. It had been reported that electrical stimulation of STN modified the activity of the pallido-nigral and subthalamo-nigral loops, and disrupted nigral astrocytic calcium excitability through an increase of glutamate and GABA releases [45], concerning the role of astrocytes in deep brain stimulation mechanisms.

Melanocortin-4 receptors on astrocytes may play important roles in the control of astrocyte activity in many brain regions. In particular, several lines of evidence confirm that of the five known melanocortin receptors only subtype 4 is present in astrocytes [46]. It was shown that MC4R signaling pathway involved the increase of cAMP production by G protein-mediated activation of adenylate cyclase [47]. Caruso, et al. reported that MC4R activation in astrocytes involved cAMP-protein kinase A (PKA) -CREB activation [48]. These results may be the experimental evidences of the receptor mechanism of melanocortinergic modulation of the astrocyte activity. It is now widely recognized that the central melanocortin system regulates energy expenditure and glucose metabolism [49-51]. The melanocortin-4 receptor (MC4R) is a G protein-coupled receptor that plays an essential role in regulating glucose homeostasis [31,52]. It is speculated that melanocortin-4 receptors on astrocytes may be tightly linked to glucose metabolism in CNS. It can clearly be seen that therapeutic mechanisms of subthalamic nucleus stimulation involve in melanocortin-4 receptor signaling on astrocytes.

**Conclusions**

Data from functional imaging and clinical neurophysiology suggests that the effects of subthalamic nucleus stimulation are not simply the result of inhibition of subthalamic nucleus activity [53]. Thereby, we think that the activity of STN and its projection pathways (such as STN- hippocampus, STN-the primary sensorimotor cortex, STN-premotor cortex, STN-parietal cortex, STN- anterior cingulate cortex, etc.) can also be modulated by deep brain stimulation. STN stimulation modulates the neuronal network rather than merely exciting or inhibiting subthalamic nuclei. Correlations with epilepsy cardinal features suggest that the improvement of specific seizure signs associated with STN stimulation might be explained by the functional modulation, not only in the target region, but also in surrounding and remote connecting areas (such as the primary sensorimotor, premotor and parietal cortex, hippocampus, anterior cingulate cortex, etc.) [Fig.1], resulting in clinically beneficial effects. It is highlighted that therapeutic mechanisms of subthalamic nucleus stimulation for refractory epilepsy may involve in melanocortin-4 receptor signaling on neurons and astrocytes.
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Conflict of Interest

The authors declare that there is no competing interest.

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Hong-Bing Xiang, et al.
Subthalamic nucleus stimulation for refractory epilepsy


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