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Mini Review Article

Excitatory Amino Acid Transporters in Parkinson's Disease: Mini-Review

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disorder of the CNS. The expression and function decreased of EAATs play an important role in PD neuronal excitotoxicity. The present mini-review aimed to briefly discuss novel findings on the roles of EAATs in the pathogenesis of Parkinson's Disease. In general, the current data are still preliminary and need more research.

Keywords: EAATs; Parkinson's disease; Movement disorders

Excitatory Amino Acid Transporter

Movement disorders (MDs) comprise a range of heterogeneous neurological diseases that include hypokinetic rigid, hyperkinetic and mixed clinical phenotypes [1-2]. Glutamate has long been known to be the predominant excitatory neurotransmitter in the central nervous system (CNS) and have been implicated in wide variety of MDs such as Parkinson's Disease (PD), essential tremor and Tourette syndrome [3]. Glutamate released from the presynaptic glutamate receptors of glutamatergic neurons enters the synapse cleft and activates the ionotropic and meta- glutamate receptors on the postsynaptic side [4]. The glutamate in the synapse cleft must be rapidly cleared and kept at a low millimolar concentration, as excessive stimulation of glutamate receptors can have toxic effects on the CNS [5-6]. Since the lack of enzyme that removing glutamate from the extracellular space, the glutamate in the synaptic cleft is mainly uptaked by a group of excitatory amino acid transporters (EAATs) [7], which consist of five different subtypes—EAAT1/GLAST/SLC1A3 [8], EAAT2/GLT-1/SLC1A2 [9], EAAT3/EAAC1/SLC1A1 [10,11], EAAT4/SLC1A6 [11], and EAAT5/SLC1A7 [11]. EAAT1 is expressed primarily in astrocytes, but also in neurons and other types of glial cells [8,12]. EAAT2 is abundantly expressed in astrocytes, neurons, and is widely distributed in the CNS [9]. EAAT3, EAAT4 and EAAT5 are mainly distributed in neurons, and the retina (EAAT5) [10-11]. EAATs are high-affinity secondary active transport proteins that mediate cellular sodium-dependent uptake of glutamate against its very high concentration gradient, using the free energy stored by co- and anti-transportions [7,11,13]. Alternatively, EAATs may regulate glutamate diffusion by adjusting the location of the metabotropic glutamate receptors to maintain accurate neurotransmission within the synapse [6-7,14]. In addition, some EAAT also act as chloride ion channels or provide cysteine or glutamate necessary for the production of reactive oxygen species scavenger glutathione [15-16]. In this review, we will discuss the role of EAATs in the pathophysiology of Parkinson's Disease. All glutamate transporters will be consistently used with their EAAT designation throughout the review for simplicity.

Parkinson's Disease (PD)

PD is a neurodegenerative disorder of the CNS, pathogenically characterized by tremor, muscle rigidity and other akinesias, shown dopaminergic neurons depletion in the substantia nigra

(SA) and formation of Lewy bodies [17]. Neuronal excitotoxicity, oxidative damage to dopaminergic neurons and glutathione depletion have been implicated in the aetiologies of PD [18-19]. Evidences confirmed that PD is associated with the decrease of glutamate transporter expression and function, reduced glutamate uptake leads to the dopamine (DA) neurons death and progressive parkinsonism symptoms [20]. The decreased expression and function of EAATs play an important role in PD neuronal excitotoxicity [3].

EAATs and PD

Studies have shown that EAAT1 expression significantly decreases at 1 and 2 weeks in the striatum of 6-OHDA lesion rats coupled with decreased mRNA expression [21-22]. EAAT1 plays a less important role in glutamate uptake in the CNS, however, it can be dramatically promoted when extracellular glutamate levels increase after EAAT2 blockade, revealing that EAAT1 may play a compensatory role in PD [23]. EAAT2-mediated glutamate reuptake is mainly responsible for glutamate uptake in the CNS. It was found that glutamate uptake was impaired and EAAT2 expression was decreased in PD animal models [24-25]. Blocking glutamate uptake with EAAT2 inhibitors reduces phosphoryltyrosine hydroxylase expression and DA synthesis [23]. Massie et al. found that EAAT2 expression increased at 3 and 12 weeks in the striatum of rats with 6-OHDA lesion [26]. EAAT3 mainly plays an antioxidant role in the pathogenesis of PD. In the EAAT3-KO mouse, dopaminergic neurons were lost in the SA, and neuronal glutathione levels are reduced, accompanied by increased oxidative stress [27]. Elevated EAAT3 expression has also been reported in PD patients. Human brain in situ hybridization showed that degenerated pigmented dopaminergic neurons expressed EAAT3 at high levels in PD patients [28]. EAAT2 blockade leads to a transient increase in EAAT1-mediated reuptake and EAAT3 expression [23]. In PD model, miR-128 may decrease the apoptosis in DA neurons and increase the expression of EAAT4 [29]. At present, there is no strong evidence for the role of EAAT5 in PD.

Some studies reported the related mechanisms of the significant changes in EAATs expression and glutamate uptake in PD models. Dopamine depletion possibly lead to post-translational modifications and promotes EAAT2 expression in partial prefrontal cortex (PFC) astrocytic. PFC dopamine depletion increases membrane expression of EAAT2 protein and glutamate uptake, but does not alter levels of EAAT1 and EAAT3, which may be involved in the compensation mechanism [30]. Moreover, EAATs are potential therapeutic targets in PD. Ceftriaxone prevents and reverses movement and neuronal deficits in PD models through upregulation of EAAT2 [31]. MiR-96-5p inhibitor could increasing the neuroprotective activity in the brain by enhance the glutathione levels via promoting EAAT3 expression [32].

Conclusions

EAATs play essential roles in the maintenance of normal excitatory synaptic transmission, protection of neurons from the excitotoxic action of excessive glutamate, and regulation of glutamatemediated neuroplasticity. There is no doubt that PD and other MDs such as essential tremor and Tourette syndrome have decreased expression and function of EAATs. However, much research is needed to clarify other aspects of EAATs in Parkinson's disease, such as the potential of EAATs as therapeutic targets. In general, the current data are still preliminary and need further research.

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Conflict of Interest

No Conflict of interest.

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