Neuroprotective mechanisms of the Rheb/mTORC1 signaling pathway in the adult dopaminergic system in vivo

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Despite intensive research effort, no effective pharmacological therapies for Parkinson’s disease (PD) have been developed. However, with the development of efficient gene delivery systems, gene therapy for PD has become a focus of research, and increasing evidences suggest that continuous production of neurotrophic factors plays a significant role in the functional restoration of the nigrostriatal dopaminergic (DA) system. We recently reported that viral vector-mediated hRheb(S16H) expression robustly induced glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) expression in adult DA neurons in vivo. Furthermore, we showed that hRheb(S16H)-induced neurotrophic factor expression was dependent on mTORC1 activity and protected nigrostriatal DA projections. Our observations suggest that hRheb(S16H) expression in mature DA neurons facilitates the production of diverse neurotrophic factors such as GDNF and BDNF, and that multiple factors are involved in the maintenance and protection of the nigrostriatal DA system in the adult brain. In this research highlight, we provide a brief overview of our most recent published findings, which demonstrate the neuroprotective mechanisms of hRheb(S16H) on nigrostriatal DA projections in vivo.

Keywords: hRheb(S16H); mTORC1; GDNF, BDNF; neuroprotection; Parkinson’s disease

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Parkinson’s disease (PD) is a chronic and progressive movement disorder that is mediated by the degeneration of nigrostriatal dopaminergic (DA) neurons, which causes motor symptoms including tremor at rest, rigidity, bradykinesia, and postural instability [¹, ²]. However, the etiology, pathogenesis, pathology, and symptoms of PD are not well understood [³]. Although the etiology of PD is poorly understood, researchers have attempted to develop targeted therapies using viral vector technologies to transfer specific genes to neurons, with the goal of improving the function of the degenerating DA system [³, ⁴]. For example, striatal delivery of adeno-associated virus 2 (AAV2)-mediated cerebral dopamine neurotrophic factor produced neuroprotective and functional restorative effects in the 6-hydroxydopamine (6-OHDA)-induced animal model of PD [⁵]. Furthermore, our previous reports demonstrated that AAV1 transduction with a gene encoding the constitutively active form of ras homolog enriched in brain (Rheb) with a mutation of the serine to histidine at the 16 position [hRheb(S16H)] induced trophic effects that resulted in the protection and restoration of DA neurons in the 6-OHDA-induced model of PD via activation of the mammalian target of rapamycin complex 1 (mTORC1) [⁶, ⁷]. Interestingly, Akt phosphorylation is decreased in the substantia nigra (SN) of PD patients, and the suppression of Akt/mTOR, a kinase that regulates neuronal survival, occurs.
in a neurotoxin-induced model of PD [8]. These results show that the activation of Akt/mTORC1 signaling may be required for the survival of DA neurons and for the functional maintenance of the DA system in the adult brain. However, it is unclear whether mTORC1 activation can induce the production of neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which are involved in neuroprotection of the nigrostriatal DA projection, in mature neurons. In a recent report, we investigated whether activation of mTORC1 by hRheb (S16H) expression in DA neurons induced the production of GDNF and BDNF, and whether the endogenous production of those factors contributed to the neuroprotection in a neurotoxin-induced model of PD [9].

Rheb, a key upstream regulator of mTORC1 activation, is regulated via GTPase activity of tuberous sclerosis complex (TSC), and it is involved in cellular processes such as protein synthesis, cell growth, proliferation, survival, and synaptic plasticity [10,11]. The serine at position 16 of Rheb has sensitivity to TSC activation, and Rheb(S16H), a mutation of the serine to histidine, exhibits resistance to GTPase activation by TSC [12]. We recently demonstrated that hRheb(S16H) expression in DA neurons of SN induced an increase in phosphorylation of the mTORC1 substrates 4E-BP1 and p70S6K, indicating activation of mTORC1, and showed apparent neurotrophic effects in the nigrostriatal DA system in the rat brains. Furthermore, hRheb(S16H) induced GDNF and BDNF expression in DA neurons, which was significantly attenuated by treatment with rapamycin (5 mg/kg), a specific mTORC1 inhibitor [13]. hRheb(S16H)-increased levels of phospho-CREB, which is involved in the production of GDNF and BDNF in neurons [14, 15], and phospho-4E-BP1 were also decreased by treatment with rapamycin. These observations suggest that the observed neurotrophic factor up-regulation may be mediated by hRheb(S16H)/mTORC1/CREB signaling pathway in DA neurons. In addition, neutralization of GDNF and BDNF prevented the protective effects of hRheb(S16H) against neurotoxins in nigrostriatal DA projections. Taken together, these observations suggest that hRheb(S16H) expression in DA neurons protects nigrostriatal DA projections through synergistic trophic effects mediated by GDNF and BDNF.

Neurotrophic factors regulate the development, maintenance, function, and plasticity of mature neurons, and they have emerged as promising therapeutic agents for PD [16-18]. Our observations demonstrated that hRheb (S16H)/mTORC1 signaling pathway induced sustained production of GDNF and BDNF, which contributed to the neuroprotective effect of hRheb (S16H) in mature DA neurons. Moreover, GDNF and BDNF expression are decreased in DA neurons from the brains of patients with PD [19, 20], and decreased Akt phosphorylation, which resulting in a loss of mTORC1 activation, is observed in the SN of PD patients [8]. Therefore, our results suggest that activation of mTORC1 by the delivery of hRheb(S16H) to DA neurons may be a promising strategy for protecting nigrostriatal DA projections in the adult brain.

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