Abstract View

ALPHA-SYNUCLEIN AND ITS MUTANTS REGULATE PLASMA MEMBRANE DOPAMINE TRANSPORTER

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alpha-Synuclein has been suggested to be involved in the pathogenesis of Parkinson's disease. Transgenic mice with altered alpha-synuclein expression exhibit impaired dopamine release and uptake. Here we confirm a previous report that showed alpha-synuclein directly binds and alters the function of the plasma membrane dopamine transporter (DAT) and extend these finding by showing the effects of synuclein mutants and the impact on MPP+ toxicity. Cotransfection of DAT with alpha-synuclein increases activity of the transporter and this effect was more pronounced with the A30P and A53T mutants. Neuroblastoma cells transfected with mutated alpha-synuclein, A30P, significantly increases uptake greater than the wild type and A53T mutant transfected cells without alteration in DAT expression. MPP toxicity was also increased with wt synuclein and the mutants but further increased MPP+ induced toxicity was not observed in A30P mutant. Furthermore, genetic reduction of DAT decreases alpha-synuclein expression. The PixCell II Laser Capture Microdissection (LCM) was used to isolate dopamine neurons from the mouse brain. alpha-Synuclein RNA levels were increased by 30% in the LCM-isolated SNc dopamine neurons in the DAT knockout mice as compared to wild type and western blot analysis revealed a 40% increase in alpha-synuclein protein in the striatum of DAT knockout mice. Thus, coregulation of alpha-synuclein and the dopamine transporter may help explain the selective vulnerability of the dopamine system in Parkinson's disease.
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