ABSTRACT

A ROLE FOR ΔFOSB IN THE REGULATION OF PARKIN IN BRAIN REGIONS CONTAINING DIFFERENTIALLY SUSCEPTIBLE DOPAMINERGIC NEURONS

By

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The hallmark pathologies of Parkinson disease (PD) are the formation of Lewy bodies and the progressive loss of nigrostriatal dopamine (NSDA) neurons. In mice, the NSDA neurons are preferentially damaged through exposure to the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Another population of DA neurons that are initially damaged by MPTP, but are able to recover are the tuberoinfundibular DA (TIDA) neurons. Parkin is a product of the PARK2 gene, which is linked to autosomal recessive or juvenile PD. Parkin has multiple functions in neurons and is predicted to protect against the neurotoxic effects of MPTP. Potential transcription factors of parkin were identified using TFSEARCH, PROMO, and Patch 1.0, and refined to 11 based the transcription factor being identified in all three programs, being known to be found in the brain, and known to respond to a type of stress that MPTP could cause. The candidate transcription factors were examined at 6 h after MPTP in regions containing the cell bodies of TIDA and NSDA neurons. From these candidates, only FosB and ΔFosB have expression patterns that mirror parkin.

Further examination of the temporal expression and cellular localization of FosB and ΔFosB after acute neurotoxicant administration were examined. Regions containing the cell bodies of the TIDA (arcuate nucleus; ARC) and NSDA (substantia nigra; SN) neurons were dissected and processed for Western blot analysis. The results reveal that expression of FosB and ΔFosB correlates with parkin, increasing in the ARC and not in the SN. Furthermore, total FosB protein was localized to nuclei of NSDA and TIDA neurons, and

expression of each FosB and ΔFosB examined in cytoplasmic and nuclear fractions derived from the ARC and SN. Though the number of DA neurons expressing total FosB does not change at 6 h post-MPTP, ΔFosB does increase in the nuclear fraction from the ARC.

AAV-mediated expression vectors were used to increase ΔFosB in the NSDA and TIDA neurons, in both cases, parkin increased about 2-fold. The dominant negative protein ΔJunD, which lacks a DNA binding domain, predominantly dimerizes with the FosBs and inhibits their ability to act as transcription factors was injected into the ARC. The AAV-ΔJunD virus blocked the increase of parkin after MPTP in the TIDA neurons. Taken together, the results support the role of FosB and ΔFosB as transcription factors of parkin, since they are predicted to bind the Park2 promoter, their expression correlates with the differential expression of parkin, increases prior to parkin, are present in nuclei of TIDA neurons, ΔFosB is sufficient to drive parkin expression, and ΔJunD blocks the increase of parkin in the ARC in response to MPTP.