

Abstract View**TYROSINE HYDROXYLASE ACTIVITY AND mRNA CHANGES IN HUNTINGTON'S DISEASE**

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Previous studies have reported significant decreases in the levels of dopamine (DA) in the brains of the R6/2 mouse model for Huntington's disease (HD). In an attempt to elucidate the catecholaminergic aberrations in HD, the activity and mRNA levels for tyrosine hydroxylase (TH), the rate-limiting enzyme in the biosynthesis of DA were determined. Enzyme activity was measured in striatal homogenates from 4, 8, and 12 week old R6/2 mice compared with age-matched littermate controls. A biphasic response in activity was observed. TH activity increased 53% in the R6/2 striatum at 4 weeks of age ($p=0.053$). We observed a 43% decrease in striatal TH activity in the R6/2 mice at 12 weeks ($p<0.001$), while no changes in TH immunoreactivity were seen. TH activity was also measured in an inducible PC12 cell model of HD. Expression of exon 1 of huntingtin (Htt) with 103 polyglutamines resulted in a significant inhibition of TH activity, with no change in TH protein levels. GST pull-down assays and immunohistochemistry revealed that TH and Htt do not appear to interact in a polyglutamine-dependent manner. We were unable to detect TH activity in human post-mortem substantia nigra (SN) from Grade 4 HD patients and controls. In situ hybridization for TH in the same subjects revealed a large decrease in TH mRNA in the SN. These changes expand the functional consequences of HD into brain regions otherwise thought to be unaffected in HD.

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