

Regulation of the protein levels of tyrosine hydroxylase by tetrahydrobiopterin in the brain.

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Dopamine is a crucial neurotransmitter to control motivation and emotion in the brain. Tyrosine hydroxylase (TH) is the rate-limiting enzyme for the biosynthesis of dopamine from tyrosine, in conjunction with molecular oxygen and a tetrahydrobiopterin (BH4) cofactor.

We found that the TH protein was decreased in the brains of newborn BH4-deficient mice, which lack the second enzyme for BH4-biosynthesis, Pts. The TH protein amount in the Pts-KO mice was restored by repeated administration of BH4 to the newborn mice. Because the Pts-KO mice die soon after birth, we made Dps-Pts-KO mice that restored the BH4 production in noradrenergic neurons. Dps-Pts-KO mice showed dystonic phenotypes with partial recovery of the TH protein in the striatum.

We investigated the other BH4-deficient mice, Spr-KO mice, which lack the third enzyme for BH4-biosynthesis. Spr-KO mice survived more than three weeks. In the brains of Spr-KO mice, the TH protein was greatly decreased as seen in the Pts-KO mice. Repeated administration of BH4 to infant mice could recover the amount of the TH protein, whereas administration of BH4 to the adult mice was ineffective. These data suggest that there should be a critical period to restore the TH protein in the brain.