PARTIAL BIOPTERIN DEFICIENCY DISTURBS POSTNATAL DEVELOPMENT OF THE DOPAMINERGIC SYSTEM

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Postnatal development of dopaminergic system is closely related to the development of psychomotor function. Tyrosine hydroxylase (TH) is a rate-limiting enzyme for the biosynthesis of dopamine, and requires tetrahydrobiopterin (BH4) as a cofactor. One of the BH4-synthesizing enzyme, sepiapterin reductase (SPR), is encoded at chromosome 2p13, where the causative gene for PARK3 located, and we reported that Spr⁻ mice exhibited bradykinesia and tremor-like phenotypes [Takazawa et al. (2008) BBRC]. Here, we examined alterations in the amounts of monoamines and the synthesizing enzymes biochemically and immunohistochemically in the brains of the mice lacking BH4-biosynthetic enzyme, SPR or 6-pyruvoyltetrahydropterin synthase (PTS). BH4 contents in Spr⁻ mice were approximately 25% of those of wild-type mice, and almost constant during P0 to P14. Dopamine content in wild-type mice was greatly increased from P0 to P14, which was in parallel with the amounts of the TH protein. Although dopamine contents of Spr⁻ mice were about 50% of the wild-type at P0, they did not show any increases of dopamine or TH protein until P14. Similar results were obtained in Pts deficient mice with some minor differences. Our results suggest that the requirement of BH4 for nigrostriatal dopaminergic system increases prominently after birth, and BH4 deficiency critically hampers the postnatal development of the dopaminergic system.