

Primate models for elucidating the circuit pathology of nigrostriatal dopamine system.

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Parkinson's disease (PD), a hypokinetic movement disorder associated with dysregulation of cortico-basal ganglia networks, is primarily caused by loss of dopaminergic innervation to the striatum. The striatum is the primary input node of the basal ganglia and the loss of dopamine innervation is caused by the death of dopaminergic neurons from the substantia nigra pars compacta. To elucidate the function of dopamine in the healthy brain, and the pathology of dopamine neuron degeneration and its normal functions, the in PD, animal models with gene manipulation of the dopamine system have become an invaluable tool with which to test different hypothesis.

Recently, we developed two primate models of PD by introducing the alpha-synuclein or tetanus neurotoxin (TeNT) into the nigral dopamine system via viral vector. This method induces either a progressive degeneration of dopamine neurons or reversible blockade of nigrostriatal dopamine transmission, respectively. In the former system, we injected the rAAV1 vector expressing wild-type alpha-synuclein into the substantia nigra of crab-eating monkeys. In these monkeys rendered parkinsonian, a battery of motor impairments was progressively manifested in the limbs contralateral to intranigral alpha-synuclein injection. The overexpression alpha-synuclein in nigral dopamine neurons led to the accumulation of alpha-synuclein in their cell bodies and neurites, and prominent loss of dopaminergic neurons from the nigra and dopaminergic terminals from the striatum.

In the latter system, we injected the lentiviral vector pseudotyped for retrograde gene transfer carrying the gene encoding tetanus toxin light chain gene downstream of the tetracycline-responsive element into the striatum of rhesus monkeys. Then, AAV vector carrying the tetracycline reverse-transactivator gene was injected into the nigra. We observed that parkinsonism-like motor deficits were induced by doxycycline administration in the monkeys injected with the vectors. These results suggest that these two primate model are useful for elucidating the pathology of PD and normal functions of the nigrostriatal dopamine system.