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Alterations related to Parkinson's disease in transgenic mice with a VMAT2-deficiency in dopaminergic neurons

Autor: Song Jiang
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. D. Bartsch

Parkinson's disease is one of the most common neurodegenerative diseases, second only to Alzheimer's disease, with about 6 million people worldwide affected. The hallmark of the PD pathology is the loss of dopaminergic neurons in substantia nigra pars compacta (SNpc). The progressive loss of dopaminergic neurons leads to a broad range of symptoms which include motor deficits like tremor, rigidity, bradykinesia, postural instability and non-motor symptoms such as hyposmia, sleep disturbances and psychiatric symptoms like anxiety, major depression, dysthymia and cognitive deficits.

The major cellular hallmarks of the pathophysiology are the Lewy bodies with deposits consisting mainly of α-synuclein, an abundant 14kDa protein. This small protein is normally expressed in the human brain and mostly localized to the presynaptic terminals. While several mutations in the α-synuclein have been. The goal of my thesis is to study the selective ablation of *Vmat2* in dopaminergic neurons.

To obtain mice with conditional ablation of *Vmat2* gene specifically in dopaminergic neurons, the Cre/loxP system was used. The mice carrying the CreERT2 (Cre recombinase and mutated estrogen receptor binding domain) under control of dopaminergic specific dopamine transporter (DAT) gene promoter were crossed with mice carrying floxed *Vmat2* gene ($VMAT2^{flox/+}$). With the injection of tamoxifen, one allele of the *Vmat2* gene in this mouse line was selectively ablated in dopaminergic neurons. While animals with ablation of both *Vmat2* alleles die soon after birth, animals with only one allele deleted survived and neurochemical and behavioral tests were studied.

In neurochemical tests, several brain regions (prefrontal cortex (PFC), nucleus accumbens (NAC), caudate putamen (CPU), hippocampus, substantial nigra/ventral tegmental area (SN/VTA) and dorsal raphe (DR) was analyzed. Using HPLC, it was clearly demonstrated in mutant $VMAT2^{-/+}$ mice that lower dopamine concentration in the hippocampus, the VTA, NAC and striatum. No significant changes of the norepinephrine and serotonin concentration was found in the mutant $VMAT2^{-/+}$ mice, demonstrating the specificity of the mouse model.

Then behavioral consequences of the selective ablation of Vmat2 gene in dopaminergic neurons were tested.

In detail, with the following tests:

Motor Behaviors
- Open Field (in dark, without stress)
- Rota-rod test
- Grip Strength test
- Beam Walking
- Footprint Analysis

Olfactory tests
- Novel Odor Exploration (non-social)
- Novel Odor Exploration (social)

Emotional Behaviors
- Anxiety (Elevated plus maze, Light/Dark box test)
- Depression-like phenotypes (Sucrose preference test, Tail suspension test)

Additional Tests
- Novel Object Recognition
- Social Interaction
- E-motion Test

The results of the thesis showed that mice with selected ablation of the *Vmat2* gene in dopaminergic neurons showed selective defect in dopamine concentration in the brain due to deficient filling of the synaptic vesicles. This dopaminergic dysfunction led to significant impairments in several motor tests and major defects in olfactory abilities, but no significant changes were found in most of non-motor tests, such as emotional performances and sleep patterns.
The conclusion of this thesis was that ablation of *Vmat2* gene in dopaminergic neurons leads to phenotypes resembling some of the major deficits in PD.