LABORATORY OF NEUROCHEMISTRY

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Our major research interest is to understand the physiological role of the dopaminergic system in animal behavior, particularly locomotion and eating behaviors, using genetically altered mice, both transgenic and gene knockout mice.

I. Role of dopaminergic transmission in locomotion and eating behavior

The dopaminergic system is implicated in the modulation of locomotor activity, the regulation of several peptide hormones in the pituitary, the modulation of synaptic plasticity and the development of neurons. The dopaminergic system is also implicated in the control of emotion, motivation and cognition. Dysfunction of the dopaminergic system can result in several neurological and psychiatric disorders, such as Parkinson's disease and schizophrenia.

In mammals, two subgroups of dopamine receptor have been identified, referred to as D1-like receptors (D1R, D5R) and D2-like receptors (D2R, D3R and D4R) on the basis of their gene structure and their pharmacological and transductional properties. D1R and D2R are the most abundantly and widely expressed in the brain and often play a synergistic role. In collaboration with Dr. Motoya Katsuki, Executive Director, National Institute of Natural Sciences, We generated *D1R/D2R* double knockout (DKO) mice and observed that *D1R/D2R* DKO mice exhibited severe impairment in locomotion, no initiation of eating, and died by 4 weeks of age.

To investigate the role of D1R in locomotor control and eating behavior, we generated transgenic mice harboring tetracycline-regulated expression of the *D1R* gene on four different backgrounds, including wild type, *D1R* KO, *D2R* KO, and *D1R/D2R* DKO. Transgenic mouse lines showed doxycycline (Dox) controllable expression of transgenic *D1R* gene.

II. Locomotor activity controlled by D1R expression

To elucidate the effects of changing *D1R* expression led by Dox administration, we applied Dox for two weeks and monitored daily locomotor activity and food/water intake (Figure 1). In *D1R/D2R* DKO background, mice exhibited decreases in locomotion and food/water intake as well as a decrease in the amount of transgene expression after Dox administration. After withdrawal of Dox administration, the mice exhibited transient hyperactivity and then recovered locomotor activity and food/water intake (Figure 2). We further analyzed locomotor activities of transgenic mice in other backgrounds and found that hyperactivity after withdrawal of Dox administration was unique to mice in *D1R/D2R* KO and *D1R* KO background, which have no endogenous *D1R* expression.

We also examined the protein expression level of D1R in the striatum of transgenic mice in *D1R/D2R* DKO background. The striatum is considered to be a major region responsible for control of locomotor activity and containing abundant *D1R* expression. During the process of recovery of locomotor activity after Dox withdrawal, the transgene D1R expression gradually increased while locomotor activity fluctuated strikingly. These results indicate that the increment of locomotor activity is not simply in proportion to the amount of D1R expression. Instead, increase of D1R expression from an abnormally low level is critical. To understand mechanisms of locomotor control through D1R signaling, we are analyzing the relationship between the *D1R* expression and altered behavior. In addition, we are investigating whether or not there is a critical period in development for the regulation of locomotion and eating behavior by dopaminergic transmission.

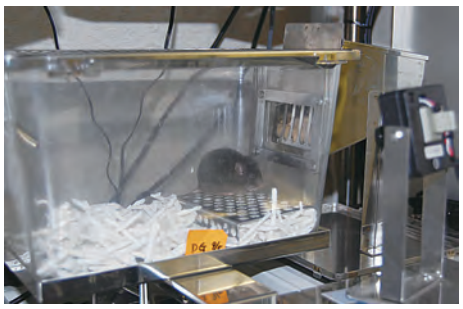

Figure 1. Experimental equipment for measurement of locomotor activity and food/water intake

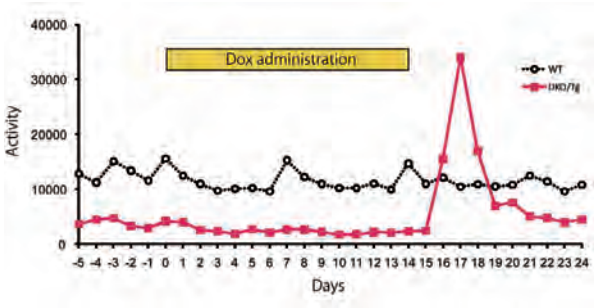

Figure 2. Locomotor activity of *D1R* transgenic mice that have *D1R/D2R* DKO background. After withdrawal of Dox administration, transient hyperactivity was observed.

Publication List

〔Original paper〕

● Tao, H., Suzuki, M., Kiyonari, H., Abe, T., Sasaoka, T., and Ueno, N. (2009). Mouse prickle1, the homolog of a PCP gene, is essential for epiblast apical-basal polarity. Proc. Natl. Acad. Sci. USA, *93*, 2110-2115.