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.

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 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 altered *D1R* expression, we applied Dox to the mice and monitored daily locomotor activity and food/water intake (Figure 1). We also examined the protein expression level of D1R in the striatum of transgenic mice. The striatum contains abundant *D1R* expression and is considered to be a major region responsible for control of locomotor activity. When Dox was continuously applied for 28 days, in *D1R/D2R* DKO and *D1R* KO background, mice exhibited decreases in locomotion and food/water intake after transgene expression decreased to a certain level. This suggests that *D1R* is required for normal activity. Next, Dox was applied for only 14 days. In this case, transgene expression was suppressed to 22%, and then allowed to increase to the original level within 7 days after withdrawal of Dox administraion. Therefore, it is possible to know the effects of an increase of D1R expression. In *D1R/D2R* KO and *D1R* KO backgrounds, which have no endogenous *D1R* expression, withdrawal of Dox administration caused transient hyperactivity (Figure 2). During the process of change in locomotor activity after Dox withdrawal, transgene *D1R* expression gradually increased while locomotor activity fluctuated strikingly. These results indicate that the level 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, we are analyzing the relationship between D1R signaling 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

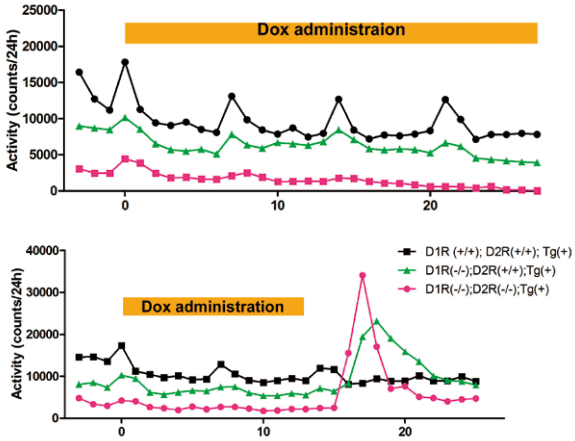

Figure 2. Locomotor activity of *D1R* transgenic mice that have *D1R/D2R* DKO and *D1R* KO backgrounds.

Publication List

〔Original paper〕

● Kusaka, M., Katoh-Fukui, Y., Ogawa, H., Miyabayashi, K., Baba, T., Shima,Y., Sugiyama, N., Sugimoto, Y., Okuno, Y., Kodama, R., Iizuka-Kogo, A., Senda, T., Sasaoka, T., Kitamura, K., Aizawa, S., and Morohashi, K.-I. (2010). Abnormal epithelial cell polarity and ectopic epidermal growth factor receptor (EGFR) expression induced in Emx2 KO embryonic gonads. Endocrinology *151*, 5893-5904.

Note: Those members appearing in the above list twice under different titles are members whose title changed during 2010. The former title is indicated by an asterisk (*).