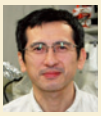
LABORATORY OF NEUROCHEMISTRY †



Professor (Concurrent)
SASAOKA, Toshikuni

Postdoctoral Fellow: *SATO, Asako*

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.

To investigate the role of D1R and D2R in locomotor control and eating behavior, we utilized D1R knockout (KO) mice, D2R KO mice, and transgenic mice harboring tetracycline-regulated expression of the *D1R* gene. Daily motor activity and food/water intake in these mice were continuously monitored in home cage environment for long term (Figure 1).

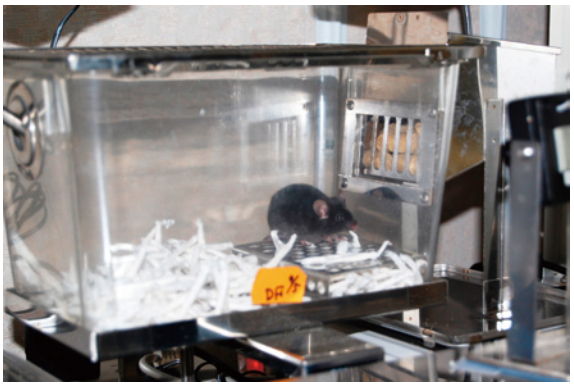


Figure 1. Experimental equipment for measurement of locomotor activity and food/water intake

II. Motor activity in D1R KO and D2R KO mice

In previous behavioral studies of D1R KO mice and D2R KO mice, changes in walking distance were analyzed in short-term sessions using beam breaks or video tracking systems. Decreased locomotor activity in D2R KO mice, and both increase and decrease in the locomotor activity in D1R KO mice have been reported in different studies. We analyzed beseline activity including all the motions (walking, rearing, grooming, climbing on the lid, and so on) in the home cages for at least 5 days. We first focused on motor activity for a 24 hr period and found that D1R KO mice were hyperactive and that D2R KO mice were hypoactive compared with wild type mice (Figure 2). To elucidate if these mice have normal circadian rhythms in activity, we analyzed motor activity in both light and dark phases. Results showed that all mice had normal circadian rhythms and that the difference in motor activity was seen during the dark phase. To further analyze the extent of activities in the dark phase, percentage of time exhibiting inactive, low, medium and high activity states were calculated. Interestingly, both D1R KO and D2R KO mice exhibited a comparable percentage of inactive state time. D1R KO mice spent more time exhibiting a high activity state, whereas D2R KO mice spent more time exhibiting a low activity state than wild type mice.

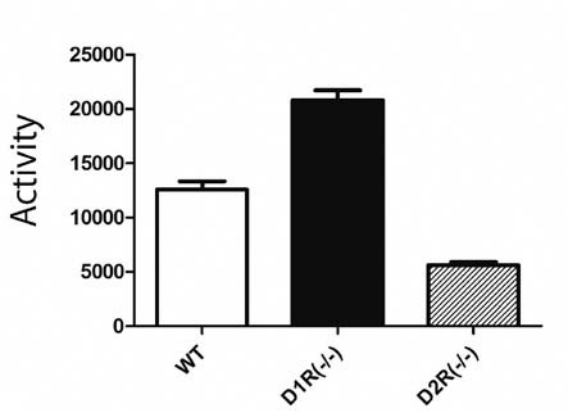


Figure 2. Motor activity of D1R KO and D2R KO mice in the home cage for 24 hr.

III. Motor activity in transgenic mice harboring controllable D1R expression

Our transgenic mouse lines showed doxycycline (Dox) controllable expression of transgenic *D1R* gene. To elucidate the effects of altered *D1R* expression, we applied Dox to the mice and monitored daily motor activity. 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 motor activity. We found decrease in activity after Dox administration in transgenic mice which had no endogenous *D1R* gene, suggesting that *D1R* is required for normal activity. When Dox was applied for only 14 days, transient hyperactivity was observed as D1R expression was increased. We are analyzing the relationship between dopamine signaling via D1R and altered behavior.

†: Professor Sasaoka ended his term as a Concurrent Professor on 31 March, 2011.