Neuropsychopharmacological study on the regulation and impairment of learning/memory and emotional behavior

○Kiyofumi Yamada
(Nagoya Univ. Grad. Sch. Med.)

To develop novel and effective anti-psychotic drugs, understanding of the mechanism for learning/memory and emotional behavior at molecular and neuronal circuit levels is essential. We have investigated the changes in gene and protein expression, protein phosphorylation and nitration, and the neurotransmitter release in discrete brain areas of animals subjected to various behavioral tasks. Furthermore, we studied a causal relationship of these molecular changes with memory and emotion, by using gene-knockout mice or specific inhibitors of target proteins. Regarding the mechanism for learning/memory, we demonstrated the involvement of the NMDA receptor/NO/cGMP and BDNF/TrkB systems in the hippocampus for spatial learning/memory and the dopamine D1 receptor/Erk1/2 signaling in the frontal cortex for recognition memory. We also demonstrated that GABAergic neurons in the lateral globus pallidus which project to the pedunculopontine tegmental nucleus play a crucial role in the regulation of prepulse inhibition of startle response, a measure of the inhibitory function and time-linked information processing. On the other hand, drug dependence is characterized by the overpowering motivational strength and the inability to control the desire to obtain the drugs. Previous studies have established an important role for the dopaminergic system in the acute reinforcing/rewarding effects of drugs of abuse. We have identified several endogenous proteins that are induced in the brain by methamphetamine and morphine and act as anti-addictive or pro-addictive factors through the regulation of dopaminergic function. TNF-a and GDNF are classified into the anti-addictive factors while tPA, MMP-2 and MMP-9 are considered pro-addictive factors.