Dopamine-induced phosphorylation of NPAS4 through MAPK regulates reward-related learning and memory

Kozo Kaibuchi¹, Yasuhiro Funahashi¹, Anthony Ariza¹, Keisuke Kuroda¹, Taku Nagai², Kiyofumi Yamada²

¹Cell Pharmacology, Nagoya University Graduate School of Medicine, Japan, ²Neuropsychopharmacology, Nagoya University Graduate School of Medicine, Japan

Medium spiny neurons (MSNs) expressing dopamine D1 receptor (D1R) or D2 receptor (D2R) are major components in striatum. In ventral striatum, D1R-MSNs compose the pathway involved in rewarding behavior while D2R-MSNs compose the pathway involved in aversive behavior. Stimulation of D1R activates protein kinase A (PKA) through Golf while D2R stimulation inhibits PKA through Gi. We have recently carried out comprehensive phosphoproteomic analysis of PKA substrates downstream of D1R and identified novel PKA substrates including Rasgrp2 (Nagai et al., Neuron 2016). Rasgrp2 is a guanine nucleotide exchange factor for Rap1 that can activate Rap1 to regulate neuronal excitability and cocaine-induced behavioral reward responses acting through Raf/MAPKK/MAPK.

On the other hand, MAPK1 may phosphorylate several transcriptional factors in nuclei, which are involved in gene expression, long-term synaptic plasticity and memory formation. However, it remains largely unclear how MAPK regulates gene expression and memory formation through D1R/PKA/Rap1 pathway. Here, we isolated and concentrated the transcriptional factors (TFs) in mouse striatum using affinity beads coated with CREB-binding protein (CBP), which acts as a transcriptional co-activator, and identified several TFs including Neuronal Per-Arnt-Sim domain protein 4 (NPAS4). NPAS4 was phosphorylated by MAPK upon D1R stimulation. The phosphorylation of NPAS4 increased the interaction of NPAS4 with CBP and enhanced the BDNF promoter activity. Furthermore, the deletion of NPAS4 in accumbal D1R-expressing MSNs impaired the cocaine-induced place preference, which was rescued with NPAS4-WT, but not with the phospho-deficient NPAS4 mutant. These results suggest that MAPK phosphorylates NPAS4 in D1R-MSNs and increases its binding with CBP, thereby regulating transcriptional activity to enhance reward-related learning and memory.