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Ph□osphorylation of Npas4 by MAPK regulates reward-related gene expression and behaviors

Yasuhiro Funahashi[1], Anthony Ariza[1], Ryosuke Emi[1], Yifan Xu[1], Shan Wei[2], Sachi Kozawa[1], Rijwan Uddin Ahammad[1], Mengya Wu[1], Tetsuya Takano[1], Yoshimitsu Yura[1], Keisuke Kuroda[1], Taku Nagai[2], Mutsuki Amano[1], Kiyofumi Yamada[2], Kozo Kaibuchi[1,3]

[1]Department of Cell Pharmacology, Nagoya University Graduate School of Medicine, [2]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, [3]Institute for Comprehensive Medical Science, Fujita Health University

Dopamine (DA) activates MAPK via PKA/Rap1 in medium spiny neurons (MSNs) expressing the dopamine D1 receptor (D1R)in the nucleus accumbens (NAc), thereby regulating reward-related behavior.However, howMAPKregulates reward-relatedlearning and memory through gene expression is poorly understood. Here, to identify the relevant transcriptional factors, we performed proteomic analysis using affinity beads coated with CREB-binding protein (CBP), a transcriptional coactivator involved in reward-related behavior. We identified more than 400 CBP-interacting proteins, including Neuronal Per Arnt Sim domain protein 4 (Npas4). We found that MAPK phosphorylated Npas4 downstream of PKA, increasing the Npas4-CBP interaction and the transcriptional activity of Npas4 at the brain-derived neurotrophic factor (BDNF) promoter. The deletion of Npas4 in D1R-expressing MSNs impaired cocaine-induced place preference, which was rescued by Npas4-WT but not by a phospho-deficient Npas4 mutant. These observations suggest that MAPK phosphorylates Npas4 in D1R-MSNs and increases transcriptional activity to enhance reward-related learning and memory. (Funahashi et al., Cell Reports, 2019)