Striatal phosphorylation signals regulating reward and aversive behaviors

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Medium spiny neurons (MSNs) are major components of the striatum, and classified into two types: MSNs expressing the dopamine D1 receptor (D1R-MSNs) or dopamine D2 receptor (D2R-MSNs). D1R stimulation activates protein kinase A (PKA) through adenylyl cyclase whereas D2R activation results in an inhibition of the cAMP/PKA signaling pathway. We have recently identified novel PKA substrates including Rasgrp2 using a comprehensive phosphoproteomic analysis of D1R pathway (Nagai et al., *Neuron*, 2016; *Trends Pharmacol Sci*, 2016). Rasgrp2 is a guanine nucleotide exchange factor for Rap1 that can activate Rap1 signaling in D1R-MSNs to regulate neuronal excitability and cocaine-induced reward responses by acting through the MAPK pathway. Among the putative PKA substrates, we have also found that Rap1 GTPase-activating protein (Rap1gap) is phosphorylated by D1R agonist or D2R antagonist (Zhang et al., *Neurochem Int*, 2019). Furthermore, adenosine positively regulates Rap1gap phosphorylation in D2R-MSNs through adenosine A2AR, while this effect is blocked by D2R agonist. The activation of PKA/Rap1/MAPK pathway in D2R-MSNs regulates aversive behaviors. Thus, both reward and aversive behaviors are controlled by PKA/Rap1/MAPK pathway in a cell-type specific manner.