

Regulation of Dopamine-stimulated cAMP by RGS20

Fejza Bala¹ and Susana R. Neves²

¹ New York City College of Technology, New York, NY

²Systems Biology Center New York and Department of Pharmacology & Systems Therapeutics, Mount Sinai School of Medicine, New York, NY

Dopamine is an essential neurotransmitter involved in memory, motor activity and reward. Dysfunction of dopaminergic neurons leads to neurological disorders such as Parkinson disease, which is a progressive neurological disorder resulting from degeneration of dopamine-producing cells in the substantia nigra causing tremors, slow movements and rigidity. Addiction is also a dopamine-related disorder. Addictive drugs such as nicotine and cocaine cause great sensitivity to dopamine, which enhances the feeling of reward. In order to understand the intracellular signaling of dopamine, we have to analyze the downstream reactions after dopamine binds to its receptor. There several types of dopaminergic receptors, that are distinguished by their coupling to the adenylyl cyclase. It is thought that dysregulation on the levels of these receptors may contribute to the pathology of schizophrenia and other diseases. D1R and D2R are G-protein coupled receptors (GPCRs) linked with the stimulatory (Gs) or the inhibitory (Gi) heterotrimeric G-proteins respectively. The striatum, located in the midbrain, expresses both types of dopamine receptors. RGS (regulators of G protein signaling) proteins are inhibitors of G protein signaling that act by activating the GTPase activity of G alpha proteins such as Gi/o. There is evidence that RGS20 levels are regulated by degradation via the ubiquitin pathway. This degradation is induced by the activation of Gi/o. The degradation is abolished upon increases of cAMP, due to PKA phosphorylation of RGS20 that protects it from undergoing ubiquitination. This type of regulation by the Gs and Gi/o pathways transforms RGS20 into a key regulator of dopamine induced-cAMP dynamics. We have created a computational model to explore the role of RGS in modulating the contribution of D1R and D2R signaling to cAMP levels. We have constrained our model with experimental data from our lab and the literature. The model 's initial prediction is that RGS levels will have a significant effect on cAMP levels.