

Temporal Integration of Dopamine and Glutamate Inputs into the Striatum

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Signaling pathways integrate multiple extracellular signals over time to modulate cellular output. Computational models allow us to recapitulate the dynamics of binding and enzymatic reactions that give rise to signaling pathways, and to predict a cell response. The striatum, a region implicated in several pathologies such as Parkinson's disease, drug addiction and schizophrenia, integrates inputs from the cortex and the ventral tegmental area. These inputs are glutamate (Glu) and dopamine (DA), key neurotransmitters involved in producing reward-dependent learning. Glu binds to its receptor mGluR, a Gq-coupled receptor on the membrane and stimulates the exchange of GDP for GTP producing active Gq-GTP. The active Gq stimulates phospholipase C (PLC), which converts PIP₂, a lipid, to diacylglycerol (DAG) and IP₃. IP₃ binds to the IP₃ receptor on the ER membrane in a cooperative manner and allows Ca⁺⁺ ions stored in the ER to flux into the cytoplasm. DAG is eventually degraded to phosphatidylcholine (PC) while IP₃ is degraded to inositol. DA binds to D1 receptor a Gs-coupled receptor. DA levels at the synapse are enhanced by exposure to drugs of abuse such as cocaine and amphetamines, since these compounds block the clearance of DA from the synapse. D1R activation leads to stimulation of adenylyl cyclase (AC) which catalyses the synthesis of cyclic adenosine monophosphate (cAMP). cAMP stimulates protein kinase A (PKA), and ultimately activates the cAMP element binding protein (CREB) in the nucleus, which is responsible for the cell's change in gene expression. Cytoplasmic increases in Ca⁺⁺ modulate the activity of adenylyl cyclase. AC5 activity is inhibited by increases in Ca⁺⁺, while AC8 activity is enhanced. We have developed a computational model of ordinary differential equations that recapitulates experimental published data. In our model we have included IP₃ generation and cytoplasmic Ca⁺⁺ increases by Glu. We have also incorporated DA- D1R dependent cAMP synthesis. We have examined the temporal integration of Glu and DA inputs at the level of DAG, IP₃, cAMP and cytoplasmic Ca⁺⁺. This approach allows us to quantitatively predict the temporal summation capacity of striatal neurons to closely spaced inputs.