

Computational Modelling of Dopamine and Glutamate Signal Integration and ERK-mediated neuroadaptation

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Dopamine plays an important role in reward-related behaviours [1, 2]. The reward or reward-predicting stimuli cause the firing of dopamine afferents converging on glutamate striatal afferents from the cerebral cortex. Thus, dopamine is not simply a nigrostriatal input, but is also a modulator of glutamate transmission, which could produce long-term effects outlasting the period of dopamine exposure.

A quantitative multi-compartment model of the dendritic spine of the striatal medium-sized spiny neuron has been constructed. Dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) is placed in the centre of this model and serves as a signal integrator through its multiple phosphorylation sites. Current efforts are focusing on how neurotransmitters affect cAMP and calcium signalling cascades, and broadcast their effects on various functions modifying spine plasticity, including the phosphorylation on calcium/calmodulin-dependent protein kinase II (CaMKII) and the activation of extracellular signal regulated kinase (ERK). The model is built-up using classical chemical kinetics; simulations are performed using E-Cell3, a software providing capabilities for hybrid stochastic-deterministic approaches [3].

ERK attracted much attention in the study of drug induced long-term neuroadaptation because of its regulatory role on transcription factors. Its activation in medium sized spiny neuron needs both the dopamine D1 receptor and the glutamate N-methyl-d-aspartate (NMDA) receptor [4], which may be mediated through DARPP-32-PP1 pathway at multiple levels. Here, we demonstrate, by computational modelling, that the striatal-enriched tyrosine phosphatase (STEP) may play a crucial role to translate DARPP-32 integrated signals into the duration of the activated ERK [5]. However, the full activation of ERK requires both Tyrosine and Threonine phosphorylation, both of which are catalysed by MAPK kinase (MEK) but dephosphorylated by a variety of protein phosphatases, including tyrosine-specific phosphatases, serine/threonine protein phosphatases, and dual specificity MAPK phosphatases [6]. Thus, in the present model, besides the known direct dephosphorylations on ERK by other phosphatases, we also plug-in possible regulatory roles of PP1 on MEK and PP2B on STEP. The fact that ERK could be phosphorylated by multiple phosphatases at multiple levels could enable it to detect the coincidence of external stimuli, then interpret them into distinct cellular responses.

A recent study suggested that during memory reconsolidation (*e.g.* re-exposure to drugs), the manipulation of the ERK pathway could reverse the established drug-related conditioning [7]. This may imply that ERK pathway plays a central role in the effects of drugs of abuse at several stages: the first administration of drugs, the drug addiction stage, and the reconsolidation stage; this may also indicate that some key regulators of ERK may change its sensibility to specific patterns of extracellular signals, which could be a potential therapeutic

strategy. Our models will allow us to quantitatively explore these effects of ERK and pave the way to generic treatments of addiction based on signalling pathways rather than specific neurotransmitter receptors or transporters.

References

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