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SYNAPTIC PLASTICITY

Timing is everything

> there is a specific time window for the spine-potentiating effect of DA

A behaviour can be reinforced if it is rewarded soon afterwards. The mechanism underlying the precise timing of this phenomenon is not known, but Yagishita *et al*. now show that dopamine (DA) regulates reinforcement-based plasticity at the single-spine level by increasing the gain of Hebbian plasticity.

The authors investigated whether DA induces structural plasticity of dendritic spines on dopamine 1 receptor (D1R)-expressing medium spiny neurons (MSNs) in mouse brain slices. Application of a spike-timing-dependent plasticity (STDP) protocol induced a small enlargement of the stimulated spines, and addition of DA during the protocol greatly enhanced this enlargement. Optogenetic stimulation of dopaminergic fibres (DA_{opto}) within 1 s after — but not 1 s before or 5 s after — the STDP protocol induced strong spine enlargement, indicating that there is a specific time window for the spine-potentiating effect of DA.

The authors established that this effect was dependent on NMDA receptors, calmodulin-dependent protein kinase II (CaMKII) and protein synthesis, as well as on D1Rs and protein kinase A (PKA). Moreover, the plasticity could be prevented by blocking the inhibition of protein phosphatase 1 (PP1) by DARPP32 (dopamine- and cyclic AMP (cAMP)-regulated neuronal phosphoprotein) and could be mimicked by inhibiting PP1. This suggests that DA-induced spine plasticity on D1R-expressing MSNs requires PKA-mediated phosphorylation of DARPP32, which results in inhibition of PP1 and, subsequently, disinhibition of CaMKII — similar to the mechanism that mediates structural plasticity of hippocampal pyramidal neurons.

DA_{opto} most strongly potentiated CaMKII activation and PKA activation when it was applied within 1 s after the STDP protocol. The authors hypothesized that the relative timing of the DA fibre stimulation and the action potentials (induced by the STDP protocol) might be detected by adenylyl cyclase 1 (AC1), as AC1 activity is induced by both D1R signalling and calcium influx through NMDA receptors; indeed, an AC1 blocker prevented PKA activation and spine plasticity.

Why does DA_{opto} (and, by extension, PKA) induce spine enlargement only within a short time window after the STDP protocol and not on its own? The authors showed that PKA activation by cAMP is normally suppressed by phosphodiesterase 10A (which degrades cAMP), the activity of which is relatively high in distal dendrites owing to their thinness.

The authors suggest that the balance between phosphodiesterase 10A activity and AC1 activity regulates cAMP levels and thereby determines the time window for the effect of DA on spine enlargement. Together, these findings point to a mechanism through which a DA 'reinforcement' signal promotes, within a very short time window, Hebbian plasticity on MSNs.

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ORIGINAL RESEARCH PAPER Yagishita, S. *et al.* A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science* **345**, 1616–1620 (2014)