論文の内容の要旨

論文題目　Dopamine D1 and D2 receptors in the nucleus accumbens regulate generalized conditioning and discrimination learning
(側坐核ドーパミン D1・D2 受容体による汎化的条件づけ・弁別学習の制御)
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Introduction

Animals survive in severe environments by learning from their experiences and adapting their behavioral strategies accordingly. One simple, yet important form of such adaptation is associative learning, whereby they learn the link between environmental stimuli and favorable outcomes. Such associative learning is thought to be mediated by prediction errors: differences between predicted and actual outcomes. Many studies demonstrate dopamine neurons change their activities according to reward prediction error: they are tonically firing (4-8 Hz), transiently activated up to 20~30 Hz (DA bursts) by more reward than predicted (positive prediction error), and transiently depressed (DA dips) by less reward than predicted (negative prediction error). This correlative link predicts the functional role of these phasic changes in dopamine neurons' activity as teaching signals to functionally drive associative learning.

The dopamine neurons mainly project to the striatum, including the nucleus accumbens (NAc), where changes in firing rate lead to bidirectional transient changes in DA concentrations. In the NAc, the primary cell type is the spiny projection neurons (SPNs), which are divided into two subpopulations, D1-SPNs and D2-SPNs, according to almost dichotomous expression of dopamine D1 and D2 receptors (D1Rs and D2Rs). It has been well established that DA bursts drive long-term potentiation (LTP) of synapses in D1-SPNs via D1Rs and reward associative learning. By contrast, a recent study using ex vivo brain slices has demonstrated that DA dips are detected by D2Rs to disinhibit LTP in D2-SPNs. In behavioral studies, optogenetic inhibition of the dopamine neurons was sufficient to induce aversive learning. However, how and for what endogenous DA dips are necessary has been unclear.

Here I established a method to optogenetically manipulate endogenous DA dips under simultaneous monitoring of DA neurons' axonal activities with fiber photometry, to investigate the functional role of endogenous DA dips in associative learning. Then, the involvement of the LTP-related signals in D2-SPNs in such learning was confirmed by drug infusion experiments and peptide expression

experiments.

Results

DA dips occurred during discrimination of generalized stimuli after reward conditioning. Drug infusion experiments showed the dependence of the generalized conditioning on D1Rs in the NAc. To test whether the observed DA dips had a causal role in discrimination learning, DA neurons were stimulated at 5 Hz under the simultaneous monitoring with fiber photometry. These stimulations overrode endogenous DA dips and inhibited the discrimination learning. Conversely, optogenetic inhibition at the timing of endogenous DA dips enhanced the DA dips and facilitated the learning. These data suggest that DA dips gate discrimination learning.

Given that DA dips in the NAc are detected by D2Rs to disinhibit LTP in D2-SPNs, which is dependent on CaMKII and adenosine A2A receptors (A2AR), I asked whether these signals in D2-SPNs were also required for discrimination learning. When autocamtide-2 inhibitory peptide (AIP), a CaMKII inhibitory peptide, was expressed in D2-SPNs at the lateral NAc core using a viral vector, discrimination learning was blocked. Also, infusion of the A2AR antagonist SCH58261 into the bilateral NAc during the discrimination period blocked discrimination learning, suggesting that these signals were required during learning.

Unexpectedly, extinction learning, another behavioral paradigm accompanied by negative prediction error, did not involve DA dips nor the LTP-related signals in D2-SPNs in the NAc.

Finally, I investigated whether D2R-dependent discrimination learning was impaired by repeated exposure to methamphetamine (MAP), which causes psychosis in humans and sensitization in mice. Treatment with methamphetamine, which dysregulated DA dips, impaired discrimination learning, while infusion of an antipsychotic, a D2R antagonist, in the NAc facilitated the learning.

Conclusion

DA dips, via the detection system by D2Rs, refine the generalized reward learning mediated by D1Rs.