This Week in The Journal

D2 Dopamine Receptors Couple to $G\alpha_s$ in Prefrontal Cortex

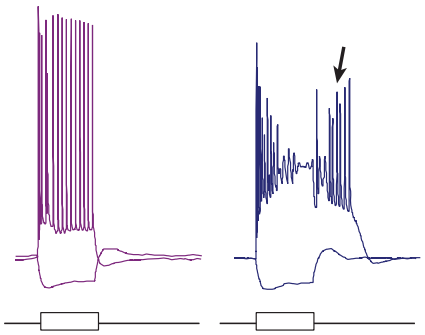
Sarah E. Robinson and Vikaas S. Sohal

(see pages 10063–10073)

Dopaminergic input to the prefrontal cortex (PFC) regulates multiple cognitive functions, including working memory, decision making, and attention. The effects of dopamine on PFC neurons depend on which type of dopamine receptor they express. Previous work (Gee et al. 2012 Neurosci 32:4959) indicated that in PFC layer 5, D2 dopamine receptors (D2Rs) are expressed selectively in a subpopulation of neurons that project subcortically (to the thalamus). Co-activation of D2Rs with NMDA receptors or L-type calcium channels altered the electrophysiological properties of these neurons, such that single depolarizing electrical pulses evoked a long-lasting afterdepolarization (ADP), during which neurons continued to spike.

Dopamine receptors are G-protein-coupled receptors that exert different effects by interacting with different $G\alpha$ subunits, as well as by interacting directly with other receptors and ion channels. In the striatum and other brain regions, D1Rs are coupled to $G\alpha_s$ or $G\alpha_{olf}$, through which they increase intracellular cAMP levels, promote the activity of protein kinase A (PKA), and increase neuronal excitability. In contrast, D2Rs are coupled to $G\alpha_i$ or $G\alpha_o$; their activation reduces cAMP levels, PKA activity, and neuronal excitability. Although D2Rs were shown to increase excitability in subcortically projecting L5 neurons in mouse PFC, Robinson and Sohal expected the receptors to exert these effects through $G\alpha_i$ or $G\alpha_o$. If this were true, PKA inhibitors should mimic the effects of D2R activation in these neurons. Surprisingly, however, this was not the case. In fact, PKA inhibitors blocked the effect of the D2R agonist quinpirole, whereas blocking $G\alpha_i$-mediated signaling had no effect. Moreover, activation of a $G\alpha_s$-coupled designer receptor produced an ADP similar to that produced by quinpirole, whereas neither $G\alpha_i$- nor $G\alpha_o$-coupled receptors produced an ADP. Finally, quinpirole did not induce an ADP in subcortically projecting neurons after D2Rs were knocked out.

These results suggest that unlike in other brain areas, D2Rs in PFC couple to $G\alpha_s$, thus promoting activation of PKA and increasing neuronal excitability. Given that D2Rs might have a higher affinity for dopamine than D1Rs, the coupling of D1Rs and D2Rs to the same G-protein might allow dopamine to increase excitability in different populations of PFC neurons depending on its concentration. How this increased excitability relates to PFC functions remains to be determined.



In the presence of NMDA and a D2R agonist (right), subcortically projecting PFC neurons fire spikes during depolarizing current pulses, as well as during an afterdepolarization (arrow) that was present after pulse termination. No afterdepolarization occurred in the presence of NMDA alone (left). See Robinson and Sohal for details.

Circadian Clock Gene Affects Pericytes, Blood–Brain Barrier

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(see pages 10052–10062)

Nearly every cell in the body exhibits circadian oscillations in gene expression and function, with 2–10% of genes being under circadian control. In each cell, oscillations are driven by the Bmal1/Clock protein complex, whose targets include genes encoding Per and Cry, which eventually inhibit Bmal1/Clock-induced transcription. Degradation of Per and Cry then allow the cycle to resume. In mammals, oscillators in each cell are synchronized by inputs stemming directly or indirectly from the suprachiasmatic nucleus, whose activity is synchronized to the daily light/dark cycle. This synchronization helps to ensure that various organ systems, such as those regulating circulation and metabolism, interact efficiently and are coordinated with daily activity cycles.

Chronic disruption of circadian rhythms has been linked to several diseases, including cardiovascular diseases, metabolic disorders, and cancer. Furthermore, dampening of circadian oscillations during aging is thought to contribute to cognitive decline and neurodegeneration. Consistent with this, deletion of *Bmal1* in most of the brain (excluding the suprachiasmatic nuclei, thus leaving sleep/wake cycles intact) led to loss of axonal terminals, as well as neuroinflammation and reactive astrocytosis (Musiek et al. 2013 J Clin Invest 123:5389). Nakazato et al. suggest these effects stem from disruption of the blood–brain barrier resulting from pericyte dysfunction.

The authors showed that knocking out *Bmal1* in nestin-expressing cells led to increased permeability of the blood–brain barrier in addition to astrocytosis and neuroinflammation. This increased permeability was accompanied by progressive loss of pericyte coverage of blood vessels in the cerebral cortex. Furthermore, expression of platelet-derived growth factor receptor β (PDGFRβ)—a protein previously shown to be required for maintenance of the blood–brain barrier—was greatly reduced in pericytes. Importantly, blood–brain barrier breakdown and astrogliosis did not occur in mice in which *Bmal1* was knocked out selectively in neurons or astrocytes, suggesting that these effects stemmed from loss of *Bmal1* in pericytes.

These results suggest that by regulating expression of PDGFRβ in pericytes, Bmal1 helps to maintain the integrity of the blood–brain barrier. They also suggest that PDGFRβ expression is under circadian control. Whether circadian oscillation in PDGFRβ leads to circadian variation in the integrity of the blood–brain barrier should be examined in future studies.

This Week in The Journal was written by Teresa Esch, Ph.D.