PERSPECTIVES

Dopamine and working memory mechanisms in prefrontal cortex

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The neural mechanisms underlying working memory – the capacity to manipulate information in short-term memory and use it to guide action – have been the subject of considerable speculation and debate for the last 30 years. The prefrontal cortex (PFC) has been the focus of studies aimed at this question since neurons there were shown to stay active during the delay period in working memory tasks, suggesting that they somehow were involved in the processing of items in memory (Fuster, 1973). In the late 1970s it became clear that working memory, and sustained activity in PFC neurons, was dependent upon cortical release of dopamine by neurons whose cell bodies were in the ventral mesencephalon (Brozoski *et al.* 1979).

But why? What was dopamine doing to PFC neurons and the circuitry there? There have been mountains of papers written on the topic and we still don't have a clear answer (Seamans & Yang, 2004). Sorting out what dopamine is doing is a particularly difficult issue for a variety of reasons but perhaps the most imposing obstacle has been that dopamine is not a conventional neurotransmitter that simply excites or inhibits neurons. Rather, dopamine works through G-protein coupled signalling cascades to modulate the gating of ion channels that orchestrate the response to classical neurotransmitters. That is, they change the way neurons respond to signals arising from other neurons to which they are synaptically connected. As a consequence, what an experimenter sees following manipulation of dopamine depends upon how the cell is interrogated or excited. Different questions produce different answers.

One particularly contentious issue has been how dopamine shapes synaptic integration in deep layer PFC pyramidal neurons. This is an important question because the sustained activity of pyramidal neurons seen in working memory tasks is thought to reflect the integration of glutamatergic synaptic inputs arising from network activity. Does dopamine promote or impede this sustained activity? Some have suggested that dopamine enhances opening of voltage-dependent Na^+ channels that help sustain activity (e.g.Yang & Seamans, 1996). The trouble with this assertion is that dopamine is thought to modulate Na^+ channels through a D1 receptor signalling cascade that results in phosphorylation of the channel by protein kinase A (PKA). But, PKA phosphorylation of the pore-forming subunit of Na^+ channels decreases open probability by promoting slow inactivation of the channels (Carr *et al.* 2003). Work with acutely isolated PFC pyramidal neurons had shown that indeed D1 receptor stimulation reduces Na^+ channel currents (Maurice *et al.* 2001). The trouble with these studies was that they could not exclude the possibility that in a neuron with intact dendrites, with an intact axon and with intact synaptic connections, things were somehow different. In this issue of the *Journal of Physiology*, an elegant study by Rotaru *et al.* (2007) puts this issue to rest. They show that in intact deep layer PFC pyramidal neurons, dopamine, acting at surface D1 receptors, diminishes active temporal 'stretching' of excitatory synaptic potentials (EPSPs) by voltage-dependent Na^+ channels. Only Na^+ channels are involved, not K^+ channels. What is more, they show that this modulation only occurs at depolarized membrane potentials. This means that the effect of dopamine is only manifested when pyramidal neurons are driven into so-called up-states by sustained excitatory input arising from the cortical network. This fits beautifully with what is known about the effects of PKA phosphorylation on Na^+ channel gating, reconciling molecular and cellular lines of study.

What does this mean for PFC activity in working memory tasks? Shortening EPSP duration tightens the requirements for effective summation and evoked spiking. In other words, D1 receptor signalling should diminish spiking in neurons receiving temporally dispersed synaptic inputs, leaving activity intact only in neurons receiving temporally coincident EPSPs. It is easy to speculate that sharpening the coincidence requirements for spike generation could be critical to appropriate sequencing of neural network activity during working memory. An unresolved question is how the modulation described by Rotaru *et al.* (2007) in the perisomatic region is coordinated with that that must be occurring in the basal and apical dendrites where dopamine undoubtedly modulates channels that influence how synaptic activity is processed.

References

Brozoski TJ, Brown RM, Rosvold HE & Goldman PS (1979). *Science* **205**, 929–932.

Carr DB, Day M, Cantrell AR, Held J, Scheuer T, Catterall WA & Surmeier DJ (2003). *Neuron* **39**, 793–806.

Fuster JM (1973). *J Neurophysiol* **36**, 61–78.

Maurice N, Tkatch T, Meisler M, Sprunger LK & Surmeier DJ (2001). *J Neurosci* **21**, 2268–2277.

Rotaru DC, Lewis DA & Gonzalez-Burgos G (2007). *J Physiol* **581**, 981–1000.

Seamans JK & Yang CR (2004). *Prog Neurobiol* **74**, 1–58.

Yang CR & Seamans JK (1996). *J Neurosci* **16**, 1922–1935.

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