HIGHLIGHTS

G-PROTEIN-COUPLED RECEPTORS

RGS puts the brakes on

Two papers published in *Neuron* give new insight into an enigmatic family of proteins — the regulators of G-protein signalling (RGS) proteins. These proteins negatively regulate G-protein signalling by increasing the rate of GTP hydrolysis by G-protein α-subunits, but their functions in the nervous system are little understood.

Both of the studies focus on RGS9, which comes in two isoforms. RGS9-1 is found in the retina and regulates the signalling cascade that is initiated by the selective interaction of photoexcited rhodopsin with activated transducin ($G\alpha_t$) bound to the γ-subunit of phosphodiesterase (PDEγ). The other isoform, RGS9-2, is expressed particularly strongly in the striatum, which lacks PDEγ. Martemyanov *et al.* investigated how RGS9-2 can specifically interact with its target G-protein subunit in the absence of this effector enzyme.

The short carboxyl terminus of RGS9-1 is crucial to its interaction with PDEγ. RGS9-2 lacks this domain and instead has a much longer carboxy-terminal domain, which shares some sequence similarity with PDEγ. Martemyanov *et al.* found that this domain seems to increase the GTPase accelerating activity of RGS9-2 in the same way as the interaction with PDEγ does for RGS9-1. However, it is unclear whether this 'affinity adaptor' is more important than localization for controlling RGS specificity, because the authors also find that RGS9-2 can strongly regulate $G\alpha_t$ even though $G\alpha_t$ is not found in striatal neurons.

But what about the function of RGS9-2 in the striatum? Rahman *et al.* provide strong evidence that it modulates signalling through D2 dopamine receptors, and speculate that it might be involved in responses to chronic drug use. They showed that RGS9-2 can act as a negative regulator of D2-receptor-induced currents in *Xenopus* oocytes that co-express inwardly rectifying potassium (GIRK) channels. *In vivo*, they found that virus-mediated overexpression of RGS9-2 in the nucleus accumbens reduces the locomotor response to D2 receptor agonists and to cocaine, whereas RGS9-2-knockout mice show increased locomotor responses to cocaine. And chronic exposure to cocaine causes an increase in the levels of RGS9-2 in the nucleus accumbens. The authors propose that this upregulation represents a compensatory adaptation mechanism that could contribute to the development of tolerance in human cocaine addicts.

There are many unanswered questions about the activities and functions of RGS proteins in the brain. Not least, exactly how RGS9-2 interacts with the D2 receptor signalling cascade remains to be unravelled. Studies that bring together the approaches used in these two papers to look at the link between molecules and behaviour should help to answer these questions.

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References and links

ORIGINAL RESEARCH PAPERS Martemyanov, K. A. *et al.* Specificity of G protein–RGS protein recognition is regulated by affinity adaptors. *Neuron* **38**, 857–862 (2003) | Rahman, Z. *et al.* RGS9 modulates dopamine signaling in the basal ganglia. *Neuron* **38**, 941–952 (2003)

FURTHER READING Burns, M. E. & Wensel, T. G. From molecules to behavior: new clues for RGS function in the striatum. *Neuron* **38**, 853–856 (2003) | Nestler, E. J. Molecular basis of neural plasticity underlying addiction. *Nature Rev. Neurosci.* **2**, 119–128 (2001)