SYNAPTIC PHYSIOLOGY

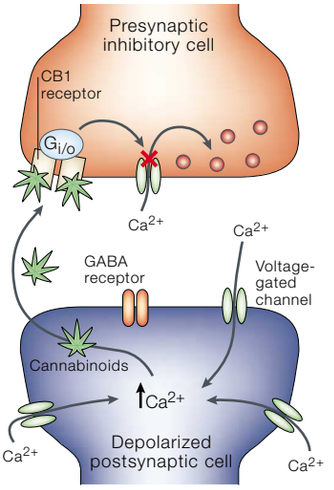
Greener on the other side

The idea that certain molecules could act as retrograde synaptic messengers has been *en vogue* for some time. Several molecules such as nitric oxide, carbon monoxide and arachidonic acid metabolites have been proposed to diffuse from the postsynaptic neuron to act on the presynaptic cell but the evidence hasn't always been incontrovertible. Three recent papers have put a new spin on the study of retrograde messengers by showing that postsynaptically released cannabinoids can inhibit transmitter release in hippocampal and cerebellar neurons.

When a hippocampal neuron is depolarized, inhibitory inputs to this cell become transiently suppressed, a phenomenon termed 'depolarization-induced suppression of inhibition' (DSI). Wilson and Nicoll focused on the mechanisms responsible for DSI in hippocampal slices and found that cannabinoids released from the postsynaptic cell transiently depress GABA-mediated transmission. The authors determined that, although cannabinoid release is Ca^{2+}-dependent, it does not seem to involve vesicle fusion, as botulinum toxin fails to block DSI.

Similarly, Ohno-Shosaku *et al.* studied DSI in cultured hippocampal neurons and found that endogenous cannabinoids were involved in synaptic suppression. Moreover, these researchers also established that strong depolarization (a stimulus that is commonly used to induce DSI) is not necessary to elicit suppression, as action-potential firing by the postsynaptic neuron was enough to produce DSI.

This form of synaptic suppression had so far been observed only at inhibitory synapses. However, Kreitzer and Regehr found that an equivalent phenomenon termed DSE occurs at excitatory synapses in the cerebellum. Depolarization of Purkinje cells can suppress parallel- and climbing-fibre input, and this suppression also depends on the action of endogenous



cannabinoids. Moreover, they showed that presynaptic Ca^{2+} influx is reduced during DSE, indicating that cannabinoids might exert their action through the inhibition of presynaptic Ca^{2+} channels. Whether a similar mechanism is also involved in DSI remains to be tested, but is a likely possibility.

DSI and DSE arguably represent the first known function of endogenous cannabinoids. In addition, these three papers provide compelling evidence for a role of cannabinoids as true retrograde messengers. But these results also give rise to many new questions. If vesicle fusion is not necessary for DSI, then how are postsynaptic depolarization and Ca^{2+} influx coupled to cannabinoid release? How do DSI, DSE and the release of endogenous cannabinoids affect hippocampal and cerebellar function? Do they interact with other forms of synaptic plasticity? Are DSE or DSI involved in the behavioural effect of marijuana? These three studies are merely the beginning of the trip.

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References and links

ORIGINAL RESEARCH PAPER Wilson, R. I. & Nicoll, R. A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* **410**, 588–592 (2001) | Kreitzer, A. C. & Regehr, W. G. Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells. *Neuron* **29**, 717–727 (2001) | Ohno-Shosaku, T. *et al.* Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron* **29**, 729–738 (2001)

FURTHER READING Montgomery, J. M. & Madison, M. V. The grass roots of synapse suppression. *Neuron* **29**, 567–570 (2001) | Felder, C. C. & Glass, M. Cannabinoid receptors and their endogenous agonists. *Annu. Rev. Pharmacol. Toxicol.* **38**, 179–200 (1998)

IN BRIEF

SYNAPTOGENESIS

Agrin-induced phosphorylation of the acetylcholine receptor regulates cytoskeletal anchoring and clustering.

Borges, L. S. & Ferns, M. *J. Cell Biol.* **153**, 1–11 (2001)

Neuromuscular-junction (NMJ) development requires agrin and the muscle-specific receptor tyrosine kinase MuSK. Does agrin-induced tyrosine phosphorylation of acetylcholine receptors (AChRs) participate in their localization at the NMJ? The authors addressed this question by expressing 'tyrosine-minus' forms of the AChR β-subunit in cultured myotubes. They found that tyrosine phosphorylation is required for AChR anchoring to the cytoskeleton and contributes to receptor clustering.

PSYCHIATRIC DISORDERS

Association between an agouti-related protein gene polymorphism and anorexia nervosa.

Vink, T. *et al. Mol. Psychiatry* **6**, 325–328 (2001)

Agouti-related peptide (AGRP) stimulates food intake and participates in the regulation of body weight. Vink *et al.* searched for *AGRP* polymorphisms in people with anorexia nervosa and identified two alleles that were significantly enriched in the patients. The authors suggest that variations in AGRP are a risk factor for the development of this eating disorder.

SENSORY SYSTEMS

Effects of membrane potential and tension on prestin, the outer hair cell lateral membrane motor protein.

Santos-Sacchi, J. *et al. J. Physiol.* **531**, 661–666 (2001)

Reciprocal electromechanical properties of rat prestin: the motor molecule from rat outer hair cells.

Ludwig, J. *et al. Proc. Natl Acad. Sci. USA* **98**, 4178–4183 (2001)

Heterologous expression of prestin confers cells with fast motility, indicating that this molecule might be the motor protein of outer hair cells (OHCs). These two papers provide additional support for this idea by showing that membrane potential and tension have similar effects on prestin in transfected cells as they do in OHCs. However, the two papers disagree on whether prestin alone has all the characteristics of the OHC motor protein or if additional proteins are required for the formation of a functional complex.

DEVELOPMENT

The winged-helix transcription factor FoxD3 is important for establishing the neural crest lineage and repressing melanogenesis in avian embryos.

Kos, R. *et al. Development* **128**, 1467–1479 (2001)

Kos *et al.* cloned the chick homologue of the transcription factor FoxD3 and found that it might serve two functions during neural-crest development. First, FoxD3 might participate in segregation of neural crest cells, as its misexpression led to the appearance of a larger neuroepithelial territory expressing neural-crest markers. Second, FoxD3 might repress melanogenesis, as knocking down its expression led to an expansion of the melanoblast lineage.