G-PROTEIN-COUPLED RECEPTORS

# Location, location, location

Position is everything, at least in the world of cell signalling. Position of molecules has long been thought to explain how a globally applied signal produces specific effects in isolated populations of cells. For example, appropriately placed adrenoceptors on cells in the heart and hippocampus mediate the increase in heart rate and altered learning ability observed after a rush of adrenaline. But these G-protein-coupled receptors (GPCRs) work by activating downstream effectors, such as ion channels, by means of second messenger cascades that are common to many of the 1,000 or so different GPCRs that are littered over the surface of a cell. So how does adrenoceptor activation lead to the targeting of specific effector systems, giving a unique response pattern? Hell and colleagues show that, for some $\beta_2$-adrenoceptors at least, the answer seems to lie in the relative positioning of the receptors and their targets.

Using immunoprecipitation from extracts of rat hippocampal neurons, the authors found that fishing for $\beta_2$-adrenoceptors resulted in co-purification of the pore-forming domain of the L-type calcium channel ($Ca_v1.2$). $Ca_v1.2$ is a specific target of $\beta_2$-adrenoceptor activation, and the result from Hell *et al.* shows that the two molecules are tightly bound together in a macromolecular complex. Moreover, the purified complex contained not just the receptor and effector, but also many elements of the intermediate signalling cascade: the G-protein subunits, the adenylyl cyclase that catalyses the formation of cyclic AMP, the cAMP-dependent protein kinase that increases the activity of $Ca_v1.2$ by phosphorylation, and a phosphatase that removes this activating group. The $\beta_2$-adrenoceptor signalling complex, therefore, seems to be preassembled in these neurons, and ready for action.

But are such complexes necessary for effective signalling? The authors addressed this question by recording the activity of $Ca_v1.2$ channels in small segments of cultured hippocampal neurons during the application of the $\beta_2$-adrenoceptor agonist albuterol. Albuterol was able to activate the observed $Ca_v1.2$ channels only when delivered to the cell through the recording electrode, but not when applied from outside to the rest of the cell. It therefore seems that albuterol-mediated activation of cAMP-dependent signalling pathways is only sufficiently robust to open $Ca_v1.2$ channels that are directly associated with $\beta_2$-adrenoceptors as part of preassembled complexes.

Not all drugs that are specific for the same type of GPCR produce the same level of cellular activation, and this latest observation might help explain how certain agonists can produce smaller responses than others, even though they are acting through the same receptors. Unlike 'full agonists', which produce maximal responses, 'partial agonists' such as albuterol might activate the subset of effectors that are closely associated with their target receptors, but be unable to drive the activation of more distant, unassociated targets. What drives the assembly of these tightly bound complexes, and how different sorts of agonist might manage to produce different levels of activation of GPCR signalling cascades, are stories for another day.

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**References and links**

**ORIGINAL RESEARCH PAPER** Davare, M. A. *et al.* A $\beta_2$ adrenergic receptor signaling complex assembled with the $Ca^{2+}$ channel $Ca_v1.2$. *Science* **293**, 98–101 (2001)
**WEB SITE** Johannes Hell's lab

## IN BRIEF

REGULATORY SYSTEMS

### Identification and characterization of a melanin-concentrating hormone receptor.

An, S. *et al. Proc. Natl Acad. Sci. USA* **98**, 7576–7581 (2001)

Melanin-concentrating hormone (MCH) is involved in the control of food intake. This paper and three others report the identification of a new MCH receptor that is expressed in hypothalamic areas known to regulate feeding behaviour. The gene for the new receptor is located in a region of chromosome 6 that is associated with cytogenetic abnormalities in obese patients, highlighting its possible involvement in this condition.

SYNAPTIC PHYSIOLOGY

### Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic $GABA_B$ responses in mice lacking $GABA_{B(1)}$.

Schuler, V. *et al*. *Neuron* **31**, 47–58 (2001)

The authors generated $GABA_{B(1)}$-knockout mice and found that the animals showed spontaneous seizures, hyperalgesia, increased motor activity and impaired learning in a passive avoidance task. More importantly, pre- and postsynaptic $GABA_B$-receptor-mediated responses were abolished. As metabotropic receptors in this class require dimerization for their function, the data indicate that $GABA_{B(1)}$ might be an obligatory component of $GABA_B$ receptors.

DEVELOPMENT

### Progressive cerebellar, auditory and esophageal dysfunction caused by targeted disruption of the *frizzled-4* gene.

Wang, Y. *et al. J. Neurosci*. **21**, 4761–4771 (2001)

Wnt signalling is involved in patterning, cell proliferation and synapse formation in the developing embryo. Wang *et al*. now report that it might also be important in later life. They deleted *frizzled-4*, which encodes a Wnt signal transducer. The adult mutant mice showed cerebellar degeneration and loss of auditory neurons, neither of which could be attributed to primary developmental defects. This implies that Wnt signalling is required for maintenance, as well as development, of the nervous system.

LEARNING AND MEMORY

### A neural correlate of working memory in the monkey primary visual cortex.

Super, H. *et al. Science* **293**, 120–124 (2001)

Super *et al.* recorded from neurons in the primary visual cortex of monkeys during a delayed-response task. In this task, the animals had to remember the position of a stimulus and make a saccade to it after a delay. Neurons that responded to the visual stimulus continued to fire during the delay period, and their activity correlated with subsequent performance. The authors propose that this activity might represent a memory trace of the stimulus.