IN THE NEWS

Winning channels

Roderick MacKinnon has been widely tipped to win a Nobel Prize for his groundbreaking work on the structure and function of ion channels — and this year he shares the Chemistry prize with Peter Agre, the discoverer of aquaporins. Unusually, the work for which MacKinnon is honoured was published just five years ago, in 1998.

As the *New Scientist* (8 October) explains: "MacKinnon's breakthrough in laying bare the structure of an ion channel for the first time was achieved by turning to a much simpler example of an ion channel than his competitors." The principles that were revealed by the structure of a bacterial potassium channel could be applied to the more complex channels found in neurons. The Nobel Academy statement said, "Thanks to this contribution we can now 'see' ions flowing through channels that can be opened and closed by different cellular signals."

On the day the prize was announced, MacKinnon was lauded by his colleagues. Talking to the *Baltimore Sun* (9 October), Christopher Miller, MacKinnon's former mentor, described him as "an offscale brilliant scientist" who has "completely changed the field." MacKinnon himself reportedly had trouble accepting the fact that he had won. He described to a press conference how he had been called at his holiday home in Cape Cod with the news. He then searched the internet but, finding no stories to confirm the news, had to wait for another call from Rockefeller. But, he said, "I wanted confirmation from Sweden. I realized after this morning that no one could reach me… I'd better buy a cell phone." (*Reuters*, 8 October.)

Rachel Jones

CELL BIOLOGY OF THE NEURON

Food and fertility

It is well known that starvation reduces fertility, and this makes sense from an evolutionary perspective because it is disadvantageous to produce large numbers of offspring when food supplies are scarce. What is the neurobiological basis of the link between feeding and fertility? Reporting in the *Journal of Neuroscience*, Sullivan *et al.* provide some new insights.

The hypothalamic gonadotropin-releasing hormone (GnRH) neurons provide a crucial neuroendocrine interface between the brain and the reproductive organs. The GnRH neurons receive input from γ-aminobutyric acid (GABA)-releasing neurons. GABA is usually an inhibitory neurotransmitter for adult neurons, but it is excitatory for GnRH neurons.

Sullivan *et al.* initially hypothesized that fasting converts the GABA-mediated excitation of GnRH neurons to inhibition. However, this was not borne out by their findings. After a 48-hour fast in female mice (which is sufficient to halt the progression of the reproductive cycle), $GABA_A$ receptor activation was still excitatory. The authors next asked whether the activity of presynaptic GABA neurons was changed by fasting. After fasting, the GnRH neurons still showed spontaneous GABA-mediated excitatory postsynaptic currents (sPSCs), but the frequency was reduced. Some GABA-releasing neurons express receptors for the satiety hormone leptin, and the authors showed that treating animals with leptin could reverse the effects of fasting on sPSC frequency.

There is also evidence that leptin potentiates the response of GnRH neurons to $GABA_A$ receptor activation. Sullivan *et al.* measured

NEURODEGENERATIVE DISORDERS

Neurodegeneration — it's a snip

Although more than one in every five patients with AIDS develops HIV dementia, the mechanisms by which infection leads to neurodegeneration are unclear. A study published in *Nature Neuroscience* provides evidence for a new neurotoxic pathway that is initiated by HIV-infected macrophages.

Zhang *et al.* found that conditioned medium from human macrophages infected with HIV was toxic to neurons *in vitro*. The medium contained elevated levels of the matrix metalloproteinase precursor pro-MMP2. When pro-MMP2 is added to a neuronal culture, it is activated on the neuronal cell surface by membrane type-1 MMP. The idea that activated MMP2 was causing the neuronal death in culture was supported by the ability of the MMP inhibitor Prinomastat to prevent neuronal death after treatment with pro-MMP2. The same group previously showed that MMP2 can cleave the chemokine stromal cell-derived factor 1α (SDF1), which is expressed by neurons and astrocytes. In the new study, they show that cleaved SDF1 binds to neuronal membranes and induces neuronal apoptosis. Pertussis toxin, an inhibitor of G-protein-coupled receptors, prevented this effect, indicating that cleaved SDF1 acts through a G-protein-coupled receptor.

To investigate whether this pathway was active *in vivo*, the authors implanted cleaved SDF1 into the striatum of mice, where it caused an increase in neuronal loss and gliosis when compared with animals treated with uncleaved SDF1 or vehicle. Similar effects were produced by implantation of conditioned medium from HIV-infected macrophages. Treatment with pro-MMP2 also produced behavioural abnormalities — specifically, the mice rotated towards the site of the

miniature PSCs (mPSCs) in brain slices from fed mice. The slices were treated with leptin, and also with tetrodotoxin to block activity-dependent signals from the presynaptic terminal. The authors found that leptin did not affect the frequency of mPSCs, but it increased their amplitude, rate of rise and decay times.

So, GABA-releasing neurons relay information about fuel availability to the GnRH neurons. The effect of leptin seems to be twofold — it promotes GABA release from the presynaptic terminal, and it makes the postsynaptic GnRH cell more responsive to GABA. It remains to be shown whether GnRH neurons express leptin receptors, although the functional data are consistent with such a possibility. Hypothalamic dysfunction is often associated with infertility in humans, and Sullivan *et al.* speculate that understanding how GABA-mediated neurotransmission is modulated in GnRH neurons could aid the development of new therapeutic approaches to treat infertility.

Heather Wood

References and links

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implantation when treated with amphetamine. This was prevented by an SDF1-neutralizing antibody or by systemic treatment with Prinomastat.

This pathway might provide new targets for therapies designed to prevent HIV-induced neurodegeneration. In particular, the authors point out that the MMP inhibitor Prinomastat is already in clinical trials for the treatment of cancer, and might be effective as a neuroprotective agent.

Rachel Jones

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AXON GUIDANCE

Follow the leader

Early in the development of vertebrate nervous systems, neurons must connect and differentiate before adopting their specific roles. To ensure this specificity, early neurons lay down an axonal scaffold that provides later axons with a track to follow. In a recent issue of *Development*, Bak and Fraser report the characteristics that differ between leader — the first axon that emerges, also known as a 'pioneer' axon — and follower axons in the developing zebrafish forebrain.

Using time-lapse fluorescence microscopy, Bak and Fraser were able to detect two distinct classes of behaviours in commissural axons. On approaching the midline, the growth rate of the leader axon slows significantly, whereas the followers maintain a fast growth rate both in and out of the midline region.

This discrepancy in growth rate between leader and follower axons coincided with differences in growth cone morphology. Leader growth cones are more complex, shorter and wider than the elongated growth cones of follower axons. The authors propose that the differences in shape and kinetics are owing to the complex midline environment that leader axons must interpret to ensue that the correct tracks are in place for subsequent follower axons. By using leader axons as guides, follower axons do not need to interpret such signals, and so are simple in shape and have faster growth rates through the midline region.

So, two types of axons engage in the building of the early neuronal scaffold, the leader axon dictating the path that follower axons take. But what happens when the leader axon is eliminated? Bak and Fraser found that, on ablation of the leader axon, the nearest follower axon adopts the role of leader, changing the shape of its growth cone and slowing down as it approaches the midline. This is reminiscent of early observations in the grasshopper, where the elimination of a guidepost cell led to its replacement by a neighbouring cell. So, two key elements in axon guidance — leader axons and guidepost cells — might enjoy some redundancy, perhaps to ensure the success of the guidance process.

Emma Green

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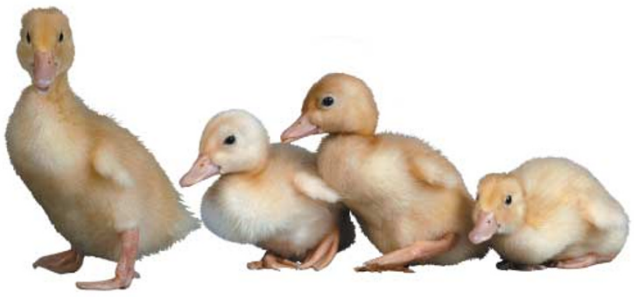

ION CHANNELS

Location isn't everything

Elevations in the intracellular concentration of Ca^{2+} can lead to the activation of transcription, and Ca^{2+} entry through L-type voltage-gated channels seems to be particularly effective in this regard. So far, this effectiveness has been explained in terms of the spatial coupling of these channels to the signalling pathways that link Ca^{2+} entry with transcription, but now Liu *et al.* challenge such a view by showing that location might not be the whole story. They report that the magnitude of the Ca^{2+} elevations through L-type channels is much larger than through other types when the increases are elicited by synaptic-like stimuli.

The authors expressed different types of recombinant Ca^{2+} channel on HEK 293 cells and examined their responses to voltage waveforms that mimicked gamma and theta bursts — forms of neuronal activity that are found *in vivo*. They observed that, at physiological temperatures, Ca^{2+} elevations mediated by L-type channels were about three times larger than the increases mediated by P/Q- and N-type channels. This effect could be explained by the stimulus-dependent inactivation of these two types of channel.

So, in addition to spatial coupling, the characteristics of synaptic activity might be important to determine the relevance of L-type channels to transcriptional activation. A crucial step to establish the true physiological significance of this mechanism will be to investigate whether Ca^{2+} channels in native neurons also show these differences in function.

Juan Carlos López

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