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

ORIGINAL RESEARCH PAPER Sullivan, S. D. *et al.* Metabolic regulation of fertility through presynaptic and postsynaptic signaling to gonadotropin-releasing hormone neurons. *J. Neurosci.* **23**, 8578–8585 (2003)

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

References and links

ORIGINAL RESEARCH PAPER Zhang, K. *et al.* HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration. *Nature Neurosci.* **6**,1064–1071 (2003)
FURTHER READING Yong, V. W. *et al.* Metalloproteinases in the biology and pathology of the nervous system. *Nature Rev. Neurosci.* **2**, 502–511 (2001)

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.

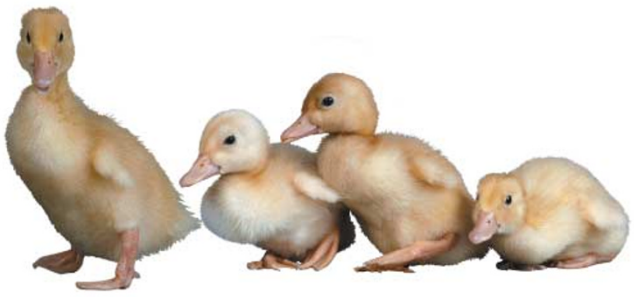
This discrepancy in growth rate between leader and follower axons coincided with differences in growth cone morphology. Leader growth cones are more complex, shorter and wider than the elongated growth cones of follower axons. The authors propose that the differences in shape and kinetics are owing to 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

References and links

ORIGINAL RESEARCH PAPER Bak, M. & Fraser, S. E. Axon fasciculation and differences in midline kinetics between pioneer and follower axons within commissural fascicles. *Development* **130**, 4999–5008 (2003)
FURTHER READING Araújo, S. J. & Tear, G. Axon guidance mechanisms and molecules: lessons from invertebrates. *Nature Rev. Neurosci.* **4**, 910–922 (2003)



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

References and links

ORIGINAL RESEARCH PAPER Liu, Z. *et al.* Decoding of synaptic voltage waveforms by specific classes of recombinant high threshold calcium channels. *J. Physiol. (Lond.)* 18 September 2003 (doi: 10.1113/jphysiol.2003.051110)
FURTHER READING West, A. E. *et al.* Regulation of transcription factors by neuronal activity. *Nature Rev. Neurosci.* **3**, 921–931 (2002)