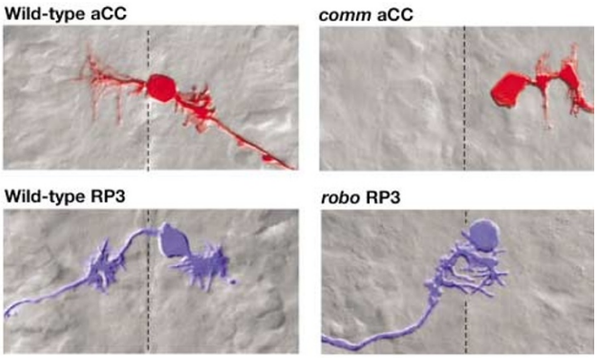
DEVELOPMENT

Dendrites need guidance too



In wild-type *Drosophila* embryos, the aCC (red) and RP3 (blue) neurons extend dendrites on both sides of the midline (dashed line). In the *comm* mutant, the aCC dendrites that normally cross the midline are lost or reduced. In the *robo* mutant, the RP3 dendrites grow towards the midline and often wrap around it. Reproduced, with permission, from Furrer *et al.*, *Nature Neuroscience* © (2003) Macmillan Magazines Ltd.

The importance of precise axon guidance for the wiring of the nervous system has long been recognized, and studies in flies and vertebrates have brought to light a multitude of molecules that allow growth cones to navigate the developing nervous system. But axons are not the only neuronal projections that need guidance, as Furrer *et al.* report in *Nature Neuroscience*. Dendrites also need to be accurately steered to their targets to make appropriate synaptic connections, and this study shows that they rely on some of the same cues as axons.

In the *Drosophila* central nervous system, two sets of molecules help to determine whether axons project contralaterally (across the midline) or ipsilaterally (away from or parallel to the midline). Slit and its receptor Robo mediate repulsion at the midline, thereby preventing axons from crossing, whereas Netrin and its receptor Frazzled mediate attraction, allowing axons to cross the midline to form commissural tracts. Furrer *et al.* asked whether these molecules also regulate midline crossing of dendrites. In addition, they studied the effects on dendritic guidance of mutations in *commissureless* (*comm*), a gene that codes for a protein that counteracts Slit/Robo-mediated repulsion.

In *comm* mutants, the number of contralaterally-projecting axons is considerably reduced. Furrer *et al.* now show that many populations of dendrites that would normally project contralaterally also fail to cross the midline in these mutants. A similar phenomenon was seen in *netrin* and *frazzled* mutant embryos. In *robo* mutants, the commissures are thickened, and it was previously thought that this was largely due to increased crossing and re-crossing of axons. However, Furrer *et al*. show that aberrant crossing of dendrites also contributes significantly to this phenotype.

The dendritic guidance defects in *frazzled* and *robo* mutants could be rescued in individual neurons by restoring the function of the corresponding gene, indicating that Frazzled and Robo act cell-autonomously to regulate the response of growing dendrites to guidance cues in their environment. The authors also found that in rescued *frazzled* mutants, Frazzled protein was found in dendrites that

SYSTEMS NEUROSCIENCE

Ghrelin on the brain

The elusive source of endogenous ghrelin in the hypothalamus is described by Horvath, Cowley and colleagues in a report in *Neuron*. Ghrelin is a peptide hormone that is produced mainly by the stomach in response to fasting. It activates the growth hormone secretagogue receptor and has powerful actions on feeding and energy regulatory circuits, including a direct influence on hypothalamic neurons. The new results indicate that at least some of these effects might be mediated by brain-derived ghrelin, rather than by ghrelin from the stomach.

Cowley *et al*. showed that ghrelin is expressed in a previously uncharacterized group of neurons in the hypothalamus. The neurons lie in the space between the lateral hypothalamic, arcuate, ventromedial, dorsomedial and paraventricular hypothalamic nuclei, and they send projections to several of these nuclei as well as outside the hypothalamus. Interestingly, the area that contains the ghrelin neurons overlaps with the projections from the suprachiasmatic nucleus, which might allow the production of ghrelin to be directly modulated by the circadian clock.

Although there have been previous indications that ghrelin is produced in the hypothalamus, the function of this brain-derived ghrelin is unclear. Cowley and colleagues have provided some clues to what it might be doing. Anatomically, they saw that ghrelin-containing boutons are often closely apposed to the axon terminals of other hypothalamic neurons, particularly those containing neuropeptide Y (NPY), raising the possibility that it might act presynaptically to modulate the release of NPY and GABA (γ-aminobutyric acid) by these neurons.

The authors went on to investigate the physiological effects of ghrelin in two hypothalamic nuclei, the arcuate nucleus and the paraventricular nucleus. They found that treatment with ghrelin increases the activity of the NPY-containing neurons to which the ghrelin neurons project, and hyperpolarizes pro-opiomelanocortin (POMC)-containing neurons in the arcuate nucleus. This hyperpolarization is probably mediated by increased release of NPY and GABA.

In the paraventricular nucleus, ghrelin reduced the GABA-mediated inhibition of 73% of neurons, but did not affect the rest. Previous work showed that NPY had the same effect, and the authors propose that the influence of ghrelin here is also mediated by a presynaptic increase in NPY release, which might in turn act presynaptically to reduce GABA secretion.

The existence of an endogenous ghrelin system in the hypothalamus might solve some of the problems that have been associated with the idea that ghrelin from the stomach acts on these nuclei to regulate energy homeostasis. If more work confirms the functions of the ghrelin-containing hypothalamic neurons, it will represent an important step in our understanding of how complex interactions between the brain and the gastrointestinal system regulate our food intake and energy expenditure.

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References and links

ORIGINAL RESEARCH PAPER Cowley, M. A. *et al.* The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron* **37**, 649–661 (2003)
FURTHER READING Inui, A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. *Nature Rev. Neurosci.* **2**, 551–560 (2001)