DEVELOPMENT

A new direction for frizzled

Wnt signalling is involved in numerous aspects of neural development, but it has not previously been implicated in axonal outgrowth. Now, Wang *et al.* have filled this gap in its functional repertoire, by showing that the Wnt receptor frizzled 3 (Fz3) is required for the development of major axonal tracts in the mammalian forebrain.

The authors knocked out the *fz3* gene in mice, and found that four axonal tracts were missing — the thalamocortical, corticothalamic and nigrostriatal tracts, and the anterior commissure, which connects the left and right hemispheres of the brain. The corpus callosum was also absent in some cases. The mutation did not seem to cause any primary defects in the proliferation or survival of neuronal precursors, so it is unlikely that the phenotype resulted simply from the loss of neurons that give rise to the axonal tracts.

Wang *et al.* asked whether the *fz3* mutation affects the intrinsic ability of forebrain neuronal precursors to develop axons. They found that, when these cells were isolated in culture, they readily adopted a typical neuronal morphology, with a full

complement of axons and dendrites. So, it is more likely that the mutation affects the neuron's ability to interpret signals from its environment. The authors suggest that Fz3 might protect the neuron against signals that inhibit axonal outgrowth.

Another clue to the function of Fz3 came from studies in *Drosophila*. The *Drosophila* Fz protein regulates cell polarity, and in the wing epithelium, it determines the point on the cell surface from which a hair will grow. Therefore, another possibility is that Fz3 could determine the direction of neurite outgrowth, perhaps by regulating the neuronal cytoskeleton. This hypothesis could be tested by examining the subcellular localization of Fz3.

These findings point to a new direction for studying Wnt signalling in neural development. It will be interesting to delve into the mechanisms by which Fz3 controls axonal outgrowth, and to find out whether any other members of the frizzled family have similar functions in other regions of the nervous system.

Heather Wood

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ADDICTION

The ups and downs of nicotine

Nicotine is often thought of as a rewarding stimulus. But it also has aversive properties, and these different motivational effects seem to be mediated by circuits that include the ventral tegmental area (VTA). Laviolette *et al.* now take a step towards unravelling these circuits, by showing that lesions of the tegmental pedunclopontine nucleus (TPP) can cause a switch in the motivational effects of nicotine infusions into the VTA, from rewarding to aversive.

The TPP receives inputs — thought to be inhibitory and mediated by GABA (γ -aminobutyric acid) — from the VTA, and sends cholinergic projections back to the VTA. Previous studies have shown that the TPP is important for the rewarding effects of several drugs. In the new study, Laviolette *et al.* infused nicotine directly into the VTA of rats, where it produced a rewarding effect, measured by

conditioned place preference. But when the TPP was lesioned bilaterally, the rewarding effect was blocked, and instead the rats showed a conditioned aversion for sites associated with nicotine infusion. TPP lesions did not block the induction of conditioned taste aversion by systemic nicotine administration — another measure of the aversive effects of nicotine.

So, it appears that the TPP is crucial for the rewarding effects of nicotine in the VTA, and that removal of the TPP reveals an aversive effect that is presumably mediated by a different circuit. The authors suggest that, whereas the aversive effects of nicotine are mediated by an ascending dopaminergic system, its rewarding effects are mediated by a non-dopaminergic pathway that includes the TPP.

Rachel Jones

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