NEUROLOGICAL DISORDERS

Shadow of perception in schizophrenia

The first description of schizophrenia as "splitting of the psychic functions" by Bleuler in 1911 has proved to be not without insight. At present, some theories propose that the basis of this disorder lies in a defect in the functional integrity of neural circuits rather than in specific brain areas or neurotransmitter systems. Reporting in the *Proceedings of the National Academy of Sciences*, Spencer and colleagues show that synchronization of neural circuits is abnormal in patients with schizophrenia and that this abnormality correlates with the core symptoms of the disease.

In this study, 20 individuals with chronic schizophrenia and 20 control subjects were asked to perform the Gestalt perception task, in which they were shown images with or without an illusory square. Patients with schizophrenia made more errors in perceiving the square and had longer median reaction times than the healthy controls. The authors used a scalp-recorded electroencephalogram to measure the brain activity of the subjects while they were performing the task. The recordings produced signals in the gamma frequency range (30–80 Hz), which is believed to be associated with the generation of an object representation and reflects rhythmic synchronization of neural discharges in a given network.

There are two types of γ-band oscillation: an early phase that is evoked by stimulus presentation, and a later phase that is associated with the response. Spencer *et al.* found that stimuli that contained an illusory square, but not those that did not, elicited the early 'stimulus-locked' oscillation in the occipital cortex of normal subjects, whereas neither stimulus evoked this oscillation in patients with schizophrenia. In contrast, the 'response-locked' oscillation was observed in the occipital cortex of both groups, although the signals in patients with schizophrenia had a different latency and a much lower frequency. Interestingly, a second response-locked oscillation was found in the parietal cortex of patients with schizophrenia, and its shorter latency and wider frequency compared with the occipital oscillation indicate that it constituted a separate effect.

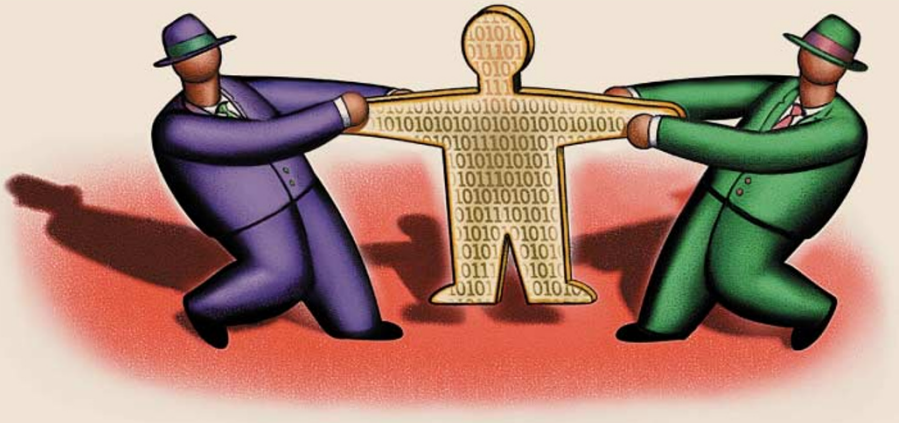
DEVELOPMENT

Occupying the middle ground

The ventral midline of the neural tube adopts a floor plate identity along most of the antero–posterior axis, except for the anterior forebrain, where it differentiates as hypothalamic tissue. In a new study reported in *Development*, Kapsimali and colleagues used a zebrafish model to investigate the molecular mechanisms that determine cell fate at the ventral midline.

The zebrafish *masterblind* (*mbl*) mutation reduces the activity of Axin1, a negative regulator of the Wnt/β-catenin signalling pathway. Kapsimali *et al.* found that in *mbl* embryos the floor plate was expanded at the expense of hypothalamic tissue. However, the hypothalamic domain could be restored by transplanting *axin1*-overexpressing epiblast cells into the prospective floor plate of young *mbl* embryos. Transplantation of these same cells into the prospective floor plate of wild-type embryos induced ectopic expression of hypothalamic marker genes at midbrain and hindbrain levels. Together, these observations indicate that induction of hypothalamic tissue at the ventral midline requires inhibition of the Wnt/β-catenin pathway.

Intriguingly, not all Wnt inhibitors seem to be equally capable of promoting hypothalamic fate. The authors tested the effects of various intracellular and extracellular Wnt antagonists, and found that the intracellular antagonists, which included Axin1, induced ectopic expression of hypothalamic markers in the ventral CNS, whereas secreted inhibitors, such as Dickkopf1, Tlc and the frizzled-related protein Frzb1, did not. So, what other properties of the intracellular Wnt inhibitors



The authors then investigated correlations between schizophrenic symptoms and these perception-evoked effects on oscillations. There was no notable correlation between the stimulus-locked oscillation and schizophrenic symptoms. However, the occipital response-locked effect correlated significantly with conceptual disorganization, visual hallucinations, thought withdrawal and global thought disorders; the parietal response-locked effect correlated with the total negative symptoms and social inattentiveness.

These findings indicate that the occipital response-locked oscillation might underlie the processes of conscious perception in response to stimuli in both healthy individuals and those with schizophrenia. Furthermore, abnormal γ-band synchrony in patients with schizophrenia might reflect neural circuit dysfunction that is related to the symptomatology of this disorder.

Jane Qiu

References and links

ORIGINAL RESEARCH PAPER Spencer, K. M. *et al.* Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc. Natl Acad. Sci. USA* 16 November 2004 (10.1073/pnas.0406074101)

FURTHER READING Engel, A. K. *et al.* Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Rev. Neurosci.* **2**, 704–716 (2001)

WEB SITE

McCarley's laboratory:
http://www.hmcnet.harvard.edu/psych/redbook/166.htm

might underlie their ability to induce hypothalamic tissue? One possible explanation comes from the finding that Axin1 seems to facilitate Nodal signalling — a pathway that is known to be required for the development of the floor plate and ventral hypothalamus. The authors found that both Nodal pathway activation and Axin1 expression promoted the insertion of cells into the ventral midline.

Kapsimali *et al.* propose that the principal role of Axin1 is to inhibit Wnt/β-catenin signalling. However, its additional effects on Nodal signalling might increase the likelihood that cells are in the right place at the right time to respond to Wnt inhibitors. The next challenge will be to identify the sources of the Wnt signals and inhibitors, so that we can obtain a clearer view of the precise sequence of events that leads to specification of hypothalamic tissue at the ventral midline.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Kapsimali, M. *et al.* Inhibition of Wnt/Axin/β-catenin pathway activity promotes ventral CNS midline tissue to adopt hypothalamic rather than floorplate identity. *Development* **131**, 5923–5933 (2004)

WEB SITE

Zebrafish research at UCL:
http://www.ucl.ac.uk/zebrafish-group/

PAIN

The GluRA, B, C of pain

It is becoming increasingly clear that synaptic plasticity in pain-sensitive pathways has many features in common with better understood forms of synaptic plasticity, such as hippocampal long-term potentiation. Now Hartmann and colleagues have shown that AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, which are vital mediators of hippocampal plasticity, are also important modulators of inflammatory pain and of synaptic plasticity in the spinal nociceptive system.

Most AMPA receptors in the central nervous system — those that contain the GluRB subunit together with GluRA, C or D subunits — have low permeability to Ca^{2+}. However, receptors that lack the GluRB subunit have much higher Ca^{2+} permeability, and many of these receptors are found in the spinal dorsal horn. AMPA receptors in the dorsal horn are also unusual in that they are found presynaptically on the axon terminals of primary sensory afferent neurons, and activation of these receptors depolarizes the afferent neurons and thereby reduces neurotransmission from afferent fibres to second-order neurons in the spine.

Hartmann *et al.* set out to investigate the possible importance of Ca^{2+}-permeable AMPA receptors in the dorsal horn in nociceptive plasticity and inflammatory pain, using mutant mice that lack the GluRA, B or C subunits. Basal levels of neurotransmission and acute responses to painful stimuli were normal in these mice, but the Ca^{2+} permeability and ion conductance properties of the AMPA receptors in the dorsal horn were not: in *GluRA*$^{-/-}$ mice there were fewer Ca^{2+}-permeable AMPA receptors and the AMPA channel currents were reduced, whereas the opposite was true in *GluRB*$^{-/-}$ mice.

To study the effects of these subunits on spinal plasticity, the authors used phosphorylation of ERK1/2 (extracellular receptor-activated MAP kinase 1 and 2) as a marker for synaptic plasticity. In wild-type and *GluRB*$^{-/-}$ mice, high-frequency activation of C-fibre inputs in the dorsal root led to increased phosphorylation of ERK1/2, but this did not occur in *GluRA*$^{-/-}$ mice (which have fewer Ca^{2+}-permeable AMPA receptors). So GluRA-containing AMPA receptors are essential for synaptic plasticity reflected by ERK1/2 phosphorylation in the spinal cord.

What is the significance of these findings for pain perception *in vivo*? Although the mutant mice showed normal responses to acute painful stimuli, *GluRB*$^{-/-}$ mice showed significantly more hyperalgesia than either wild-type or *GluRA*$^{-/-}$ mice in a model of chronic inflammatory pain that involved injecting the hindpaw with an irritant. Moreover, in a test of rapid sensitization of pain pathways, *GluRA*$^{-/-}$ mice showed less sensitization and *GluRB*$^{-/-}$ mice showed more.

The results of this study show that the GluRA and GluRB subunits of AMPA receptors, which control the Ca^{2+} permeability of the receptors and can also influence their trafficking and synaptic availability, have opposing effects on synaptic plasticity in spinal pathways *in vitro* and on inflammatory pain *in vivo*. These findings add to our understanding of pain perception, and might help to drive the development of treatments for chronic pain conditions.

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Hartmann, B. *et al.* The AMPA receptor subunits GluR-A and GluR-B reciprocally modulate spinal synaptic plasticity and inflammatory pain. *Neuron* **44**, 637–650 (2004)

FURTHER READING Collingridge, G. L. *et al*. Receptor trafficking and synaptic plasticity. *Nature Rev. Neurosci.* **5**, 952–962 (2004)