

SENSORY SYSTEMS

Itching to explain

Itch sensations — for example, those produced by a mosquito bite — are familiar to us all. In most cases, itch is a temporary annoyance that might prompt action to avoid the cause in the future. But for people suffering from clinically intractable itch as a result of atopic dermatitis, liver disease or immune system disorders, it is a serious problem. However, a lack of understanding of the neural nature of itch has hindered the development of adequate therapies. So the discovery by Andrew and Craig of a class of itch-specific spinothalamic tract (STT) neurons, described in *Nature Neuroscience*, is an important breakthrough.

An itch-specific neural pathway has long been an attractive hypothesis to explain itch, but results to support this idea have been elusive. The first evidence was provided by the identification in humans of primary afferent C-fibres that selectively responded to histamine (the best-known itch inducer in skin) in a manner that parallels the sensation of itch. These neurons were insensitive to mechanical and thermal stimuli, and had very low conduction velocities. Andrew and Craig reasoned that if itch is a specific sensation, then the specificity of histamine-selective primary afferent fibres should be represented centrally.

Lesion studies have indicated that the pathway for itch — like that for pain — involves the STT, which projects to the thalamus. STT neurons are located in lamina I of the spinal cord. By implanting thalamic electrodes in anaesthetized cats, the authors activated and thus identified lamina I STT neurons that projected to the thalamus. They then categorized these neurons according to their response to mechanical and thermal stimulation of their innervation area in the skin. Most were conventional nociceptive-specific, thermoreceptive-specific or polymodal nociceptive neurons, but a small fraction (17/190) showed no response at all (14) or only a weak response to noxious heat (3). The activity of each of the insensitive neurons was monitored when hista-



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mine was applied to their innervation area, and ten were excited with a response pattern that corresponded to the histamine-sensitive C-fibre activity in humans and the accompanying itch sensations. Conventional STT neurons did not show this response. The itch-specific neurons also differed in other physiological properties — they had low conduction velocities, did not show spontaneous activity and projected predominantly to the lateral thalamus. These data indicate that the identified itch-specific neurons constitute a functionally and anatomically distinct group of STT neurons that provides a central neural substrate for itch.

Furthermore, it was shown that these itch-specific neurons were monosynaptically activated only by C-fibres with very low conduction velocities similar to those of the histamine-selective C-fibres in humans. So it seems that itch is mediated by specific peripheral and central pathways. Interestingly, various observations indicate that itch pathways interact with those for pain — for example, scratching inhibits itch and opiate administration reduces pain but can cause itch. Further understanding of itch pathways and their interactions will hopefully lead to new treatments for clinically intractable itch.

Peter Kirkpatrick

 **Links and references**

ORIGINAL RESEARCH PAPER Andrew, D. & Craig, A. D. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nature Neurosci.* **4**, 72–77 (2001)
FURTHER READING Schmelz, M. *et al.* Specific C-receptors for itch in human skin. *J. Neurosci.* **17**, 8003–8008 (1997) | Hunt, S. P. & Mantyh, P. W. The molecular dynamics of pain control. *Nature Rev. Neurosci.* **2**, 83–91 (2001)

IN BRIEF

NEUROPATHOLOGY

The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling.

Nicole, O. *et al.* *Nature Med.* **7**, 59–64 (2001)

Although tissue-plasminogen activator (TPA) is used to treat ischaemic stroke, negative effects of this protein have also been reported. Here the authors highlight the ambivalence of TPA as a therapeutic agent by showing that TPA cleaves the NMDAR1 receptor subunit, enhances NMDA-induced Ca^{2+} influx and increases cell death. As neuron depolarization can induce TPA release, their data also indicate that endogenous TPA might potentiate the excitotoxic damage seen after episodes of ischaemia.

SYNAPTIC PHYSIOLOGY

Fine tuning of an auditory synapse for speed and fidelity: developmental changes in presynaptic waveform, EPSC kinetics, and synaptic plasticity.

Taschenberger, H. & von Gersdorff, H. *J. Neurosci.* **20**, 9162–9173 (2000)

The calyx of Held synapse participates in sound localization. The accuracy of this synapse depends on its rapid and sustained function, but recordings from the calyx before the onset of hearing had shown synaptic depression upon repetitive activity. The authors explored whether the calyx undergoes functional changes around the onset of hearing and found several modifications that would favour synaptic speed while preventing depression: action potentials became briefer, excitatory synaptic currents were faster and the releasable pool of synaptic vesicles increased in size.

DEVELOPMENT

The autoregulation of retinal ganglion cell number.

González-Hoyuela, M. *et al.* *Development* **128**, 117–124 (2001)

During eye development, retinal ganglion cells (RGCs) regulate their own number through a negative feedback signalling loop, and the molecules involved are beginning to be identified. The authors showed that nerve growth factor (NGF) is one of the molecules involved in this loop. They found that, in the developing chick, RGCs secrete NGF, which limits further RGC differentiation and kills any ganglion cells that migrate into the retina.

CELL BIOLOGY OF THE NEURON

Oligomerization of opioid receptors with β_2 -adrenergic receptors: a role in trafficking and mitogen-activated protein kinase activation.

Jordan, B. A. *et al.* *Proc. Natl Acad. Sci.* **98**, 343–348 (2001)

The formation of G-protein-coupled heteromeric receptors results in functional changes in the interacting partners. Here the authors show that δ -opioid and β_2 -adrenergic receptors can form heteromers, and that heteromer formation affects membrane trafficking of the complex. This is a novel example of the functional effects of heteromerization, and show that receptors coupled to stimulatory and inhibitory G proteins can form complexes.