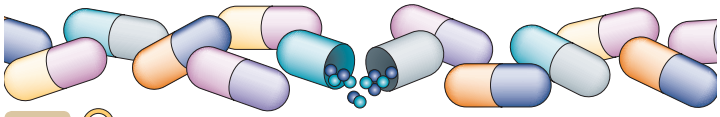

PAIN

Stressing pain relief

How is it that a soldier in the heat of battle, or a sportsman caught up in a crucial match, can keep going despite injuries that would normally be cripplingly painful? New insights into how stressful situations can make us less sensitive to pain come from a study by Hohmann and colleagues. They find that the release of endogenous cannabinoid compounds is crucial for this effect, termed stress-induced analgesia.

Cannabinoids, such as 2-arachidonoylglycerol (2AG) and anandamide, are endogenous substances that act through cannabinoid 1 receptors (CB1) in the brain. Agonists of these receptors have an anti-nociceptive effect, and antagonists enhance nociception, which indicates that endogenous cannabinoids might also be anti-nociceptive. Hohmann and colleagues therefore investigated whether endocannabinoids are involved in opioid-independent stress-induced analgesia.

In the rat model of stress-induced analgesia, the stressful event is an electric shock to the foot, after which the rats' sensitivity to pain is measured using a tail-flick test. Normally, the electric shock reduces pain sensitivity, and this effect does not require opioid peptides. However, when the authors treated the rats with a CB1 antagonist, the anti-nociceptive effect was greatly reduced, which supports the idea that endocannabinoids are at least partly responsible for stress-induced analgesia. To test the idea further, the authors gave a cannabinoid agonist to rats every day for two weeks, so that they became tolerant to its effects. After this regime, not only were the analgesic effects of cannabinoid agonists reduced, but stress-induced analgesia was also decreased.

Which parts of the brain are involved in this effect? The existing evidence points towards the activation of pathways from the amygdala to the midbrain periaqueductal grey, brainstem and spinal cord. When Hohmann *et al.* injected a CB1 antagonist into the dorsolateral periaqueductal grey, stress-induced analgesia was greatly reduced. More evidence for the importance of the midbrain came from measurements of endocannabinoid levels: after the footshock, both anandamide and 2AG were upregulated in the midbrain, but not in other parts of the brain, such as the occipital cortex. Interestingly, though, these two endocannabinoids showed different timescales of upregulation: 2AG concentrations increased rapidly, within 2 min of the footshock, whereas anandamide concentrations peaked 7–15 min after the shock.

To investigate whether the rapid release of 2AG mediates stress-induced analgesia, the authors developed an inhibitor of monoacylglycerol lipase (MGL). MGL hydrolyses 2AG and thereby deactivates it. Injection of the MGL inhibitor into the periaqueductal grey (which would be expected to increase the concentrations of 2AG) enhanced the anti-nociceptive effect of stress. Inhibitors of the enzyme that deactivates anandamide, fatty acid amide hydrolase (FAAH), also enhanced stress-induced analgesia. These results are consistent with the idea that, in the periaqueductal grey, both 2AG and anandamide mediate the analgesic effect of stress.

As well as increasing our understanding of intrinsic anti-nociceptive mechanisms in mammals, these results might point towards the use of MGL or FAAH inhibitors as possible therapeutic agents for the treatment of pain.

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Hohmann, A. G. *et al.* An endocannabinoid mechanism for stress-induced analgesia. *Nature* (in the press; doi:10.1038/nature03658)

FURTHER READING Piomelli, D. The molecular logic of endocannabinoid signalling. *Nature Rev. Neurosci.* **4**, 873–884 (2003)

IN BRIEF

DEVELOPMENT

The boundary cap: a source of neural crest stem cells that generate multiple sensory neuron subtypes.

Hjerling-Leffler, J. *et al. Development* **132**, 2623–2632 (2005)

The boundary cap is a group of neural crest-derived cells that gives rise to neurons and glia in the dorsal root ganglion. Ernfors and colleagues have now shown that these cells can self-renew and that their fate as neurons or glia depends on the stage of embryonic development. After neuronal differentiation, single boundary cap stem cells can spontaneously generate various subtypes of nociceptive and thermoreceptive neuron that are present only in the spinal and cranial nerve ganglia. These findings identify boundary cap cells as a source of truly multipotent neural crest stem cells that can give rise to several subtypes of functional peripheral sensory neuron.

SLEEP

The neural substrates of infant sleep in rats.

Karlsson, K. Æ. *et al. PLoS Biol.* **3**, 891–901 (2005)

Unlike adults, sleeping infants do not show clear state-dependent changes in cortical electroencephalographic activity. This has led to proposals that sleep in infants is more primitive than adult sleep, and that it depends on diffuse activation in the CNS rather than the more specific circuits that mediate adult sleep. However, Karlsson and colleagues have now shown that sleep in infant rats is characterized by periods of muscle atonia and myoclonic twitching that resemble those seen during adult sleep, and that the medullary inhibitory area that is required for the expression of atonia is part of a circuit that includes the subcoeruleus, pontis oralis and dorsolateral pontine tegmentum. Neurons in these areas show patterns of state-dependent activity that are similar to the neural basis of sleep in adults.

NEUROTRANSMITTER RECEPTORS

G protein-dependent presynaptic inhibition mediated by AMPA receptors at the calyx of Held.

Takago, H. *et al. Proc. Natl Acad. Sci. USA* **102**, 7368–7373 (2005)

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors (AMPARs) mediate ionotropic excitatory synaptic transmission in the mammalian CNS. However, these receptors can also interact with secondary messenger signalling pathways in neurons. Takago and colleagues use patch-clamp recordings at the giant nerve terminal of the calyx of Held to show that AMPARs are expressed presynaptically at this site and mediate metabotropic presynaptic inhibition by interacting with specific G proteins. The G-protein activation reduces glutamatergic transmission by inhibiting voltage-gated Ca^{2+} currents in the nerve terminal. AMPARs have also been reported to be expressed presynaptically at several other types of nerve terminal, and might, therefore, regulate presynaptic glutamate release at other sites.