ANALGESIA

Lipid linked to improved opiate therapy

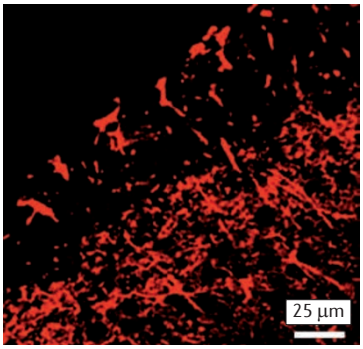

Image courtesy of D. Salvemini, Saint Louis University School of Medicine, Missouri, USA.

> Spinally formed sphingosine 1-phosphate (S1P) has a key role in opioid tolerance as well as opioid-induced hyperalgesia.

Opiates such as morphine are the most effective treatments for severe pain. However, patients often become tolerant to these drugs, requiring increasingly high doses for effectiveness, and this leads to dependence, over-sedation and other side effects. Now, Salvemini and colleagues have shown that spinally formed sphingosine 1-phosphate (S1P) has a key role in opioid tolerance as well as opioid-induced hyperalgesia (hypersensitivity to pain) and that inhibitors of the production and activity of S1P could have the potential to address these limitations of opioid therapy. Furthermore, as reported in *The Journal of Neuroscience*, they find that S1P acts in two ways on spinal glial cells: it causes both inflammatory cytokine release and post-translational nitration of enzymes thought to be involved in sensitization to pain.

S1P is produced from ceramide by the sphingosine kinases SPK1 and SPK2 and is the end product of the ceramide metabolic pathway. S1P acts on cells throughout the body, including neurons and glia in the central nervous system. Several S1P inhibitors are known to have anti-inflammatory effects — one example is fingolimod (Gilenya; Novartis), which was recently approved for the treatment of multiple sclerosis. From their previous studies, the authors knew that ceramide biosynthesis is associated with morphine tolerance, but it was not known whether the ceramide–S1P pathway is involved. To test this in rats, the authors co-administered morphine and a sphingosine kinase inhibitor (either DMS or SK-I) and found that morphine-induced tolerance and hyperalgesia — as assessed by the time taken to respond to painful stimuli — were significantly reduced.

The authors also found that the rats that developed tolerance and hyperalgesia following morphine administration had higher levels of S1P, as measured in spinal extracts of sphingolipids. Spinal ceramide, measured by immunofluorescence, was similarly elevated in these animals and colocalized with markers for two kinds of glia (microglia and astrocytes) but not with markers for neurons. DMS prevented these effects and also prevented a morphine-induced increase in the inflammatory cytokines tumour necrosis factor, interleukin-1β and interleukin-6, which are thought to be involved in neuronal excitability.

In addition to these anti-inflammatory effects, DMS attenuated a morphine-induced increase in peroxynitrite in the rats' spines. Peroxynitrite can nitrate two glial cell proteins thought to have a role in the sensing of pain — GLT1 and glutamine synthetase (GS) — deactivating them as a result. Their deactivation is thought to enhance glutamate neurotransmission, which is important in central sensitization and might therefore play a part in the development of hyperalgesia. The morphine-induced nitration of these proteins was reduced by DMS, establishing a link between S1P and the peroxynitrite-mediated nitration of GLT1 and GS.

This study is significant because of the large number of patients who could potentially benefit from improved pain management with opiates by co-administering agents that target S1P production or its effects. However, precisely how morphine boosts ceramide levels and how S1P modulates inflammatory cytokines and causes protein nitration remain to be discovered.

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ORIGINAL RESEARCH PAPER Muscoli, C. *et al.* Counter-regulation of opioid analgesia by glial-derived bioactive sphingolipids. *J. Neurosci.* **30**, 15400–15408 (2010)
FURTHER READING Brinkmann, V. *et al.* Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nature Rev. Drug Discov.* **9**, 883– 897 (2010) | Woolf, C. J. Overcoming obstacles to developing new analgesics. *Nature Med.* **16**, 1241–1247 (2010)