ANALGESICS

Just what we wanted

For thousands of years, opioids have been our front-line defence against severe pain, but given that their use is accompanied by the unwanted side effect of dependence and the development of tolerance, alternative analgesic approaches are desperately needed. A paper in the latest issue of *Neuropharmacology* offers the promise of such a novel strategy, in the form of highly selective and efficacious agonists at the 5-hydroxytryptamine (5-HT)$_{1A}$ receptor.

Francis Colpaert and his team have been seeking alternatives to opioids for the past quarter century, basing their search around a concept that any perturbation of nociceptive systems produces dual effects, which are opposite in nature (see Further Reading below). Thus, opioids are known to deliver analgesia in the short term, but this gives way to hyperalgesia in the long term — the phenomenon of tolerance. Could a class of compounds be found that would reverse this sequence, initially inducing pain but giving rise to long-lasting analgesia?

Searching for leads that could counteract opioid analgesia led them to look at the 5-HT$_{1A}$ receptor, and this new report focuses on the properties of F 13640, a novel methyl-amino-pyridine 5-HT$_{1A}$-receptor agonist with nanomolar affinity and exceptionally high selectivity. F 13640 also has greater efficacy than other known 5-HT$_{1A}$-receptor agonists, and the authors speculate that it is this combination of efficacy, potency and selectivity that lends it its analgesic properties.

The Randall and Selitto technique, which quantifies nociception by measuring the vocalization threshold to acute mechanical stimuli, was used to show that in normal rats, F 13640 produces hyperalgesia followed by analgesia (the reverse of what is seen after morphine injection). In rat models of chronic neuropathic pain, in which the level of pain is assessed by monitoring the oral self-administration of the opioid analgesic fentanyl, two-week infusion of F 13640 was shown to decrease fentanyl self-administration (FSA). Interestingly, three other centrally acting analgesics in clinical use (imipramine, ketamine and gabapentin) failed to inhibit FSA, as did the less efficacious 5-HT$_{1A}$-receptor agonist, 8-OH-DPAT.

The study was extended to monitor the analgesic effects of F 13640 in models of hyperalgesia produced by nerve damage. In rats with spinal-cord injuries, F 13640 produced lasting analgesia, manifested as an increase in the vocalization threshold to stimulation. Furthermore, over the two-week infusion period, Colpaert and colleagues observed a time-dependent decrease in one particular measure of hyperalgesia; sensitivity to von Frey hair-cell stimulation. This raises the exciting possibility that F 13640 administration might result in the development of 'inverse tolerance', with analgesia getting more, not less, potent with time.

The acute hyperalgesia seen in normal animals on F 13640 administration might indicate a potential problem for introducing the compound into the clinic. However, it seems that when nociceptive stimulation is considerable, as in the case of chronic neuropathic pain, F 13640 produces analgesia without any initial pain, in keeping with the dual-effect concept.

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References and links

ORIGINAL RESEARCH PAPER Colpaert, F. C. *et al.* Large-amplitude 5-HT$_{1A}$ receptor activation: a new mechanism of profound, central analgesia. *Neuropharmacology* **43**, 945–958 (2002)

FURTHER READING Colpaert, F. C. System theory of pain and of opiate analgesia: no tolerance to opiates. *Pharm. Rev.* **48**, 355–402 (1996)