Gender-specific responses reveal untapped potential of κ-opioids

κ-Opioids have been available for clinical use for more than four decades and studies have shown that women prefer them to morphine for coping with labour pain. However, many clinical studies have failed to demonstrate significant pain-killing properties. In the past five years, a team led by Jon Levine at the University of California (San Francisco, CA, USA) has produced data suggesting that κ-opioids might have untapped potential. Their work shows that men and women have very different responses to κ-opioids[1]. Experimental data from the study also suggests that co-administration of the opioid-receptor antagonist naloxone with a low dose of the κ-opioid nalbuphine produces profound and long-lasting analgesia in both sexes. 'In the past, many studies have not taken account of gender differences – data showing that κ-opioids have limited analgesic potential probably came from trials made up mostly of men, who we now know respond poorly to κ-opioids,' observes Levine.

The present study builds on an observation made by Levine in 1988 that a marked analgesia could be induced in men by administration of a low dose of naloxone and the κ-opioid pentazocine (for general information on opioids, see Box 1). 'This was before we started looking for different responses between men and women, so the effect of gender was not considered,' says Levine. In the

light of more recent data showing that another κ-opioid, nalbuphine, could increase the pain levels experienced by men but not women[2], Levine's team investigated the interaction between naloxone and low doses of nalbuphine.

The study

A total of 56 patients, who had just undergone surgery to remove impacted molars, were given an injection of either naloxone (0.4 mg) alone, naloxone plus nalbuphine (5.0 mg), nalbuphine alone, or a placebo. Each person rated their pain levels on a visual analogue scale (VAS): zero was no pain, 10 cm indicated the worst pain imaginable. Patients were given their injection when they indicated a pain rating >2.5 cm along the scale. The pain rating of each patient at the time of injection was taken as the baseline pain intensity. VAS ratings were then recorded every 20 min, starting 10 min after the first injection.

As expected, men given nalbuphine alone experienced more pain than men given placebo. Naloxone alone did not result in a significant decrease in perceived pain in men but significant analgesia resulted from co-injection of nalbuphine with naloxone. In women, injection of nalbuphine or naloxone alone produced effects similar to those seen with the placebo, but naloxone and nalbuphine combined produced analgesia, and this was slightly more marked than that seen in men[3].

'The potential implications of this finding are incredible,' says Levine. κ-Opioids, given at low to moderate

Box 1. Opioids and their receptors

Opioids work by activating opioid receptors that bind endogenous opioid peptides – the endomorphins, enkephalins and dynorphins. The μ-, δ- and κ-opioid receptors were discovered in the mid-1980s, and a fourth, orphanin FQ came to light in the mid-1990s when the original three were cloned (Table 1). Morphine, the most potent synthetic opioid acts as an agonist of the μ-opioid receptor, but has lower affinity

Table 1. The major endogenous and synthetic ligands, and synthetic antagonists for the four opioid receptors

	Receptors			
	μ	**δ**	**κ**	**ORL1**
Endogenous agonists	β-Endorphin Endomorphins	Methionine Enkephalin	Dynorphin	Nociceptin/ orphanin FQ
Synthetic agonists	Morphine	DPDPE	Bremazocine	–
Antagonists	Naloxone	Natrindole, Naloxone	Naloxone	$NC(1–13)NH_2$

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doses, are only minimally addictive, in stark contrast to morphine-based opioids. 'The two other major side effects of morphine – tolerance and constipation – also do not occur with κ-opioids,' he adds. If κ-opioids can be given in combination with naloxone to induce analgesia equivalent to that obtained using morphine, the comparative lack of side effects would make κ-opioid therapy a much safer option.

'This is a very interesting study,' comments Anthony Dickenson, Professor of Pharmacology at University College (London, UK). 'It raises questions about the extent that gender differences contribute to the effects of other analgesics, or indeed other drugs with CNS actions. Clearly, this study could lead to a reappraisal of drugs acting on other pharmacological targets,' he adds.

Possible mechanism of action

The reason for the different responses is not yet known but Levine speculates that action at different κ-opioid receptor subtypes might be important. 'The anti-analgesic effect of nalbuphine might be mediated by a subset of κ-receptors that are sensitive to naloxone antagonism. Thus, naloxone might unmask the analgesic effect of nalbuphine by antagonizing this anti-analgesic effect,' explains Levine. Men might have more of the naloxone-sensitive κ-opioid receptor subtype than women. 'The effects of naloxone suggest that nalbuphine might have a complex pharmacology – whether all the observed effects are explicable by κ-opioid receptor subtypes needs to be determined,' points out Dickenson.

Future studies

Levine and colleagues are now engaged in follow-up studies to examine the analgesic potential of the κ-opioid/naloxone combination in different types of pain and to investigate how people respond to it for chronic, long-lasting pain. As both drugs are approved for use independently, Levine expects that a combi-nation therapy could be used in clinical practice 'shortly', but he also anticipates that the new findings will renew enthusiasm for developing new κ-opioid drugs. 'The field of κ-opioid analgesics has been a big mess for some time and this could begin to set it straight,' he concludes.

REFERENCES

1 Gear, R.W. *et al.* (1996) Significantly greater analgesia in females compared to males after κ-opioids. *Nat. Med* 2, 1248–1250

2 Gear, R.W. *et al.* (1999) The κ-opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with post-operative pain. *Pain* 83, 339–345

3 Gear, R.W. *et al.* (2000) Naloxone reveals separate gender-dependent analgesic and antianalgesic effects of nalbuphine in humans. *J. Pain* 1, 122–127

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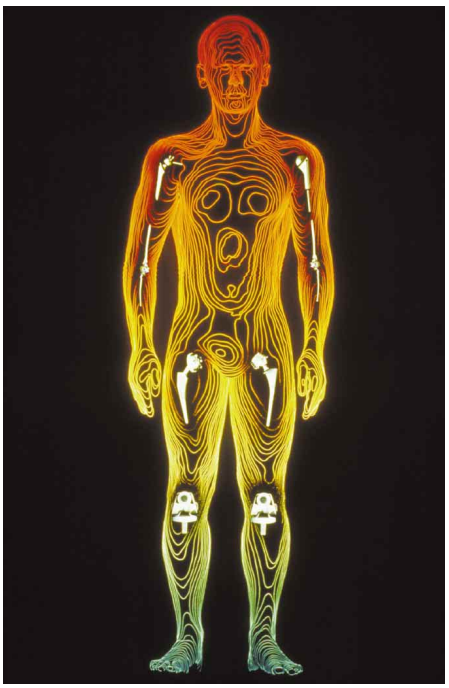
Virtual drug resistance testing in HIV

A new computer-based technique will enable doctors to obtain rapid and accurate information on drug resistance patterns among strains of the HIV. The technique – Virtual Phenotype – was developed by Virco Laboratories (Cambridge, UK). It comprises a large database of both genotype and phenotype information on several thousand HIV variants, together with software to match test HIV samples with those already in the growing database.

Multidrug treatment for HIV reduces viral load and inhibits viral replication. However, viral mutations confer drug resistance to single antiretroviral therapies and cross-resistance to others. Such resistance is a major cause of treatment failure in patients infected with HIV and the problem is rising



rapidly. Although confirmed epidemiological data are not yet available on HIV resistance, 'Approximately 70% of HIV strains isolated from treated patients are resistant to at least one class of anti-HIV drugs. There are clear signs of resistance in newly infected people, which shows that resistant strains are also being transmitted,' says John Mellors (Chief of the Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA).

'The Virtual Phenotype system is a simple matching process that compares the genotype of an HIV sample with that of a large number of variants in the company's database. The difference between this and other resistance testing techniques is that it enables the rapid interpretation of genetic information to find out which drugs are most likely to

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