Recent advances in opioid pharmacology

Opioids produce analgesia but also respiratory depression, dependence and a variety of other troublesome side effects. With this in mind, several alternatives to opioids in the treatment of pain have been suggested and used effectively, as have different ways of using opioids. Despite this, the clinical holy grail of quality analgesia without respiratory depression has yet to be attained.

This issue of the *British Journal of Anaesthesia* results from a meeting held at Leicester University in September 1997 – the Eighth International Symposium of Pain and Anaesthesia – at which several leading authorities gave up-to-date reviews on new developments in opioid pharmacology and speculated on future research. Their talks are the basis of articles in this issue, which also includes topical reviews on the pain/opioid theme and, to keep the issue as current as possible, abstracts associated with the symposium “Recent Advances in Opioid Pharmacology” held on the first day of the meeting. Since September last year there have been important further developments, some of which are noted below.

In the past 5–6 years our understanding of opioid pharmacology has advanced monumentally, as a result of the simultaneous cloning by Evans and colleagues and Kieffer and colleagues of the δ opioid receptor (named DOR). The studies that followed (reviewed in articles 4–7) have led many of us to question our understanding and basic beliefs of opioid pharmacology. For example, what of opioid receptor subtypes? We all know that respiration is depressed when large doses of opioid are given to humans. This observation, coupled with the pharmacology of drugs like naloxonazine and the dermorphin analogue TAPS, led to the description of μ1 and μ2 subtypes of μ opioid receptors, with the former mediating analgesia and the latter producing respiratory depression. The cloning of the μ opioid receptor (MOR), which followed cloning of the κ receptor (KOR), does not lend support to the existence of separate μ1 and μ2 subtypes. Do these receptors result from post-translation modification of a common protein? This remains to be determined. To add to this confusion the existence has been proposed, using antisense oligonucleotide technology, of a morphine-6-glucuronide receptor. Studies of this type were again prompted by publication in 1992 of the DOR sequence by Evans and colleagues and Kieffer and colleagues. So what message can be gleaned from these studies? First, that opioids surely produce analgesia and respiratory depression. Second, that the structural and pharmacological studies do not tie up. Third, we can be sure that morphine acting at the μ receptor produces analgesia, as Brigitte Kieffer’s group in Strasbourg have generated a μ knockout mouse (a mouse engineered to lack μ opioid receptors) in which morphine does not produce analgesia. In an attempt to unify opioid receptor classification, the International Union of Pharmacology (IUPHAR) has reclassified opioid receptors as OP1, OP2 and OP3 (table 1). The μ receptor story took a further interesting turn in 1997 when endorphins 1 and 2 were described. These peptides display extremely high affinity and selectivity for μ opioid receptors and have recently been identified in human brain. Endorphins 1 and 2 produce spinal analgesia and supraspinal analgesia in mice. Endorphin 1 and 2 reduced C-fibre and Aδ-fibre (endomorphin 1 only) responses after i.t. administration in rats. In common with other opiates, endorphins inhibit Ca2+ entry through voltage-sensitive Ca2+ channels (in NG108 cells) and inhibit cAMP formation in cells expressing recombinant μ opioid receptors. In addition, and in common with other μ opioids, endorphins 1 and 2 decrease cardiac output and total peripheral resistance and produce hypotension in rats and rabbits. The clinical significance of these peptides in anaesthesia and pain management will need careful evaluation.

A fascinating new receptor–transmitter system, the orphan opioid receptor–nociceptin/OFQ, has recently been identified. The receptor, often termed ORL1, is found in the pain pathway but does not bind conventional opioids. The endogenous peptide nociceptin, or orphanin FQ, produces a range of effects in animals including analgesia, hyperalgesia and anti-opioid actions but this is controversial (see also this issue). To help resolve the controversy, studies using the recently described orphan-receptor knockout mouse will be invaluable. In January of this year Guerrini and colleagues described the first antagonist for the orphan receptor with affinity at the peripheral-type receptor, and in March Okuda-Ashitaka and colleagues reported the isolation, from prepronociceptin, of nocistatin, which appears to reverse nociceptin action. Further detailed studies with these peptides will clearly add to our understanding of this system in vitro and in vivo.

As well as these advances in basic pharmacology there is also continuing interest and research into the use of opioids in the clinical setting, some aspects of

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—I would have everie man write what he knowes and no more.”—Montaigne
which are covered in this issue. These include introduction of the plasma-esterase-metabolized opioid remifentanil, the emerging use of peripherally acting opioid antagonists such as methylnaltrexone\textsuperscript{26-27} and exploration of novel routes of opioid administration.

I hope that the articles in this issue may stimulate readers to enter a fascinating area of research, and also that the clinical holy grail\textsuperscript{1} of quality analgesia without respiratory depression can become a reality.

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References

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