The kappa opioid receptor is associated with the perception of visceral pain

Abstract

µ-, δ- and κ-opioid receptors are widely expressed in the central nervous system where they mediate the strong analgesic and mood-altering actions of opioids, and modulate numerous endogenous functions. To investigate the contribution of the κ-opioid receptor (KOR) to opioid function in vivo, we have generated KOR-deficient mice by gene targeting. We show that absence of KOR does not modify expression of the other components of the opioid system, and behavioural tests indicate that spontaneous activity is not altered in mutant mice. The analysis of responses to various nociceptive stimuli suggests that the KOR gene product is implicated in the perception of visceral chemical pain. We further demonstrate that KOR is critical to mediate the hypolocomotor, analgesic and aversive actions of the prototypic κ-agonist U-50,488H. Finally, our results indicate that this receptor does not contribute to morphine analgesia and reward, but participates in the expression of morphine abstinence. Together, our data demonstrate that the KOR-encoded receptor plays a modulatory role in specific aspects of opioid function.

Comment

Morphine, the major active component of opium, has been used for centuries for the alleviation of pain. Use of morphine results in many side effects and the misuse of its derivatives such as heroin is obvious to all. Nevertheless, morphine mimetics are a potentially useful treatment option for pain, and identification of those without side effects is a major therapeutic goal. This has looked more likely with our increased understanding of the biology of the opioid receptors.

Based on pharmacological and molecular criteria, three different receptor classes (µ, δ and κ) mediate the activity of opioids. All belong to the G protein coupled seven transmembrane class of receptors which mediate a wide variety of effects. These receptors have distinct but overlapping distribution patterns in the body. Molecular cloning and the development of selective agonists and antagonists have done much to aid our understanding of opioid biology. However, as none of the agents developed so far can be considered truly specific for a particular opioid receptor, definitive proof of the role(s) of particular receptor types in health and disease is lacking. Transgenic technology may overcome this deficiency. Using this technology, mice deficient in each of the µ- and δ-opioid receptors have now been generated. In animal studies, κ-opioid receptor agonists are potent analgesic agents with fewer side effects and potential for misuse. The precise role of these receptors is unclear, but the recent report of a κ-opioid deficient mouse has highlighted the potential selective analgesic role of these receptors in the gastrointestinal tract.

Using a standard gene targeting approach, Simonin et al disrupted the first 79 amino acids of the N-terminal region of the κ-opioid receptor. As with the other gene knockouts of the opioid ligands or receptors (table 1), deletion of the gene had no effect on normal embryonic development, nor were there any gross abnormalities. However, when the expression of the κ-opioid receptor in regions of the brain was investigated using the tritiated high affinity κ-opioid receptor ligand, CI-977, there was total loss of κ-opioid binding sites in the homozygous and 50% loss in the heterozygous animals compared with the wild type mice. There were no differences in the endogenous expression of the µ- and δ-opioid receptors or opioid peptides, indicating that there were no compensatory changes in these mice. The κ-opioid deficient mice then underwent a series of

Table 1  Gene knockout mice for opioid receptors and ligands

<table>
<thead>
<tr>
<th>Gene disrupted</th>
<th>Development</th>
<th>Phenotype (homozygous)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-endorphin</td>
<td>No effect</td>
<td>No overt locomotor or behavioural changes; no analgesic response to swim stress</td>
<td>Rubinstein and colleagues⁷</td>
</tr>
<tr>
<td>Pre-pro-enkephalin</td>
<td>No effect</td>
<td>Altered locomotor activity</td>
<td>Koning and colleagues¹</td>
</tr>
<tr>
<td>µ-opioid receptor</td>
<td>No effect</td>
<td>Increased pain perception to a variety of pain stimuli</td>
<td>Mattes and colleagues⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altered locomotor activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altered anxiety response</td>
<td></td>
</tr>
<tr>
<td>δ-opioid receptor</td>
<td>No effect</td>
<td>Response to thermal pain abolished</td>
<td>Zhu and colleagues⁴</td>
</tr>
<tr>
<td>K-opioid receptor</td>
<td>No effect</td>
<td>Normal response to visceral chemical pain</td>
<td>Simonin and colleagues</td>
</tr>
<tr>
<td></td>
<td>No effect</td>
<td>No effect on locomotor activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety response normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal response to thermal, chemical and mechanical pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased response to visceral chemical pain</td>
<td></td>
</tr>
</tbody>
</table>
behavioural tests representing stressful and non-stressful conditions. In each test the \( \kappa \)-opioid receptor knockout mice exhibited a similar phenotype to the wild type mice.

Important differences, however, were noted in tests of nociception. In tests involving external body site—thermal (tail flick, hot plate), mechanical (tail pressure) or chemical (formalin) stimuli—there were no differences in the responses of \( \kappa \)-opioid deficient mice compared with wild type. In notable contrast, \( \kappa \)-opioid deficient mice exhibited a dramatic increase in their responsiveness to a visceral pain stimulus (intraperitoneal injection of acetic acid) compared with wild type. This spectrum of activity is different to \( \mu \)-knockout mice—such animals exhibit changes in nociceptive responses to thermal but not visceral agents. This suggests a role for \( \kappa \)-agonists in the control of visceral pain.

U-50,488H is a widely used and selective \( \kappa \)-agonist. The analgesic, but not all of the behavioural, effects of this compound were abolished in the knockout mice. This suggests that subtypes of \( \kappa \)-opioid receptors may exist. Results of pharmacological studies have also indicated that there may be \( \kappa \)-opioid receptor subtypes and that U-50,448H has high affinity for the proposed \( \kappa \)-1 subtype. The existence, however, of these proposed subtypes has yet to be proved at the molecular level.

In conclusion, Simonin et al’s study provides the first molecular evidence that there are distinct differences in the in vivo functions of the \( \mu \)- and \( \kappa \)-opioid receptors. More importantly, it is clear that the \( \kappa \)-, and not the \( \mu \)-, opioid receptor is involved in the perception of visceral pain. We await the full characterisation of the \( \delta \)-opioid receptor knockout mouse and the molecular characterisation of additional \( \kappa \)-opioid receptor subtypes. It will be important to characterise the \( \kappa \) knockout mice further with other forms of visceral nociception, such as colorectal distension, and also to investigate whether the well known diuretic effects of \( \kappa \)-agonists are present in these animals.

Abdominal pain is one of the key distinguishing features of the irritable bowel syndrome and may be related to increased sensory afferent signals emanating from the gut wall. Previous studies in animals have highlighted that \( \kappa \)-agonists can inhibit visceral pain and suggested that peripheral rather than central receptors were involved. A major challenge will be to elucidate the site of action of these agents and assess whether these are underpinned by differing \( \kappa \)-opioid receptor subtypes. Visceral pain is also associated with a wide variety of disorders including inflammatory bowel disease and dyspepsia. This suggests that specific targeting of \( \kappa \)-opioid receptors may open up new therapeutic opportunities in the treatment of pain associated with disorders of the gastrointestinal tract.

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