Opioids and central sensitisation: I. Pre-emptive analgesia

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Abstract

Opioids are powerful analgesics when used to treat acute pain and some forms of chronic pain. A large body of literature has shown that opioids can, in addition, also prevent (this review) or induce and perhaps reverse [Ruscheweyh and Sandku¨hler, Eur. J. Pain, in press, doi:10.1016/j.ejpain.2004.05.011] some forms central sensitisation in in vitro and in vivo animal models of pain. However, the concept of central sensitisation is, at present, ambiguous and the usefulness of opioids as pre-emptive analgesics in human pain patients is still not clear.

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1. What is “central sensitisation”?

In analogy to sensitisation of nociceptive nerve endings in peripheral tissues, the enhanced responsiveness of nociceptive neurons in the central nervous system, e.g., during inflammation or trauma, has been termed “central sensitisation”. This phenomenon has been most intensively studied in spinal dorsal horn (Woolf, 1983; Sandkühler, 2000; Willis, 2002). While sensitisation of nociceptors is a well established peripheral mechanism leading to allodynia and hyperalgesia, the concept of central sensitisation is not quite as straightforward (Cervero and Laird, 1996). For example a phenomenon such as an increase in the size of low threshold mechanoreceptive fields of spinal wide-dynamic range neurons during inflammation has been considered a sign of central sensitisation. However, neither is the role of wide-dynamic range neurons for hyperalgesia or allodynia known, nor is an increase in low-threshold mechanoreceptive fields an established model of abnormal sensitivity to pain. One would rather expect that such a change in receptive field size would lead to a decrease in mechano-sensory spatial resolution (e.g. measured in humans as an increased two-point discrimination threshold). Many studies on central sensitisation, including our own, were performed on superficial spinal dorsal horn neurons with an unknown role in nociception. About 30–40% of the neurons in spinal laminae I and II are inhibitory and an increase in the responsiveness of inhibitory nociceptive neurons may well lead to a stronger feed-back inhibition and thus antinociception rather than to allodynia or hyperalgesia.

Another proposed mechanism of central sensitisation is “wind-up”. When C-fibres are electrically stimulated at a frequency between 0.3 and 3 Hz, some spinal neurons respond to the first 10–30 stimuli with an increasing number of actions potentials (“wind-up”), often followed by a decrease in number of action potentials per stimulus (Herrero et al., 2000). This is a normal coding feature of some nociceptive spinal dorsal horn neurons and not per se a sign of sensitisation (Woolf, 1996). Under normal conditions “wind-up” will facilitate nocifensive responses during the first 10 s of a sustained C-fibre
barrage, which is a meaningful protective mechanism. Sensitisation of spinal dorsal horn neurons may cause an enhanced “wind-up” response and this increased “wind-up” rate is a potential indicator, rather than a mechanism of central sensitisation.

Sprouting of Aβ-fibres into superficial laminae of spinal dorsal horn has been suggested to contribute to allodynia following nerve injury. However, after nerve injury, C-fibres take up tracers that are normally taken up selectively by A-fibres. The resulting labelling of superficial laminae by the tracer after nerve injury therefore does not indicate Aβ-fibre sprouting (Hughes et al., 2003). On the other hand, excitatory Aβ-fibre input to superficial spinal dorsal horn is facilitated following nerve injury (Kohno et al., 2003), possibly due to disinhibition of polysynaptic pathways. Once again, increased sensory input to superficial spinal dorsal horn neurons does not necessarily imply enhanced nociception. Thus, if all these phenomena are collectively labelled “central sensitisation” then the analogy to peripheral sensitisation would be quite misleading. There are, however, some mechanisms that may more likely contribute to enhanced pain sensitivity following inflammation or nerve injury:

1.1. Loss of inhibition

Some evidence suggests that inflammation or nerve injury leads to loss of GABAergic (Coul et al., 2003) and/or glycinerge (Müller et al., 2003) inhibition in spinal dorsal horn. It is presently not known whether selective death of inhibitory interneurons e.g., by apoptosis, or diminished efficacy of inhibitory transmission is involved. In any case this loss of spinal inhibition may well contribute to allodynia and hyperalgesia as pharmacological blockade of GABAergic or glycinerge spinal inhibition induces severe allodynia and hyperalgesia in behaving animals (Dickenson et al., 1997).

1.2. Dorsal root reflexes

There is some evidence to suggest that tactile allodynia which is caused by peripheral neuropathy is mediated by an abnormally strong pre-synaptic effect of spinal GABAergic interneurons on spinal terminals of nociceptive C-fibres. Normally, low threshold Aβ-fibres excite GABAergic interneurons which in turn pre-synaptically inhibit nociceptive transmission from primary afferent C-fibres onto second-order neurons. This inhibition is believed to involve depolarisation of the C-fibre terminals. In case of neuropathy, the pre-synaptic depolarisation may become sufficiently strong to evoked actions potential discharges in C-fibres (dorsal root reflexes). This then triggers rather than inhibits neurotransmitter release from C-fibres. Thereby impulses in low threshold Aβ-fibres gain excitatory access to nociceptive pathways leading to touch-evoked pain (Cervero and Laird, 1996; Cervero et al., 2003).

1.3. Synaptic long-term potentiation

Recently, considerable progress has been made in understanding central mechanisms of hyperalgesia and alldynia. A small group of neurons has been identified in lamina I of spinal dorsal horn that is necessary for full development of hyperalgesia and alldynia following inflammation and peripheral nerve injury (Nichols et al., 1999). These neurons express the NK1 receptor for substance P and most project to supraspinal sites. Electrical stimulation of dorsal root afferents at C-fibre strength enhances synaptic strength (synaptic long-term potentiation, LTP) between primary afferent C-fibres and these projection neurons, but not other nociceptive lamina I neurons for prolonged periods of time (Ikeda et al., 2003). LTP can also be induced in superficial spinal dorsal horn in vivo by natural noxious stimulation (Sandkühler and Liu, 1998). LTP induction requires co-activation of glutamate receptors of the NMDA-type and NK1 receptors. Several independent lines of evidence suggest that LTP in superficial spinal dorsal horn is a cellular mechanism of central sensitisation leading to hyperalgesia. Induction mechanisms, pharmacology and signal transduction pathways of spinal LTP and some forms of centrally mediated hyperalgesia are virtually identical (Sandkühler, 2000).

2. μ-Opiate receptor agonists prevent some forms of central sensitisation

2.1. Loss of inhibition

There is some evidence that δ- but not μ- or κ-opiate receptor activation may protect neocortical neurons from glutamate excitotoxicity (Zhang et al., 2000). This is also a potential mechanism of injury-induced cell loss in spinal dorsal horn. It is, however, not known whether opioids pre-empt inflammation- or nerve injury-induced loss of inhibition in spinal dorsal horn. Evidence for the contrary was, however, found: chronic opioid application lead to an apoptotic cell death of spinal GABAergic neurons (Mao et al., 2002).

2.2. Synaptic LTP

In a rat in vivo model surgical levels of anaesthesia by volatile anaesthetics (sevoflurane, isoflurane or halothane) failed to prevent induction of spinal LTP. Systemic application of low doses of the clinically used μ-opiate receptor agonist fentanyl did, however, prevent LTP
induction (Benrath et al., 2004). Synaptic LTP was also blocked in vitro by the selective μ-opiate receptor agonist DAMGO, probably by inhibition of glutamate release (Terman et al., 2001). In addition μ-opiate receptor agonists post-synaptically inhibit spinal neurons that express the NK1 receptor (Aicher et al., 2000) which could also prevent LTP induction in these neurons.

2.3. Animal behaviour

A number of behavioural animal studies have shown that systemic or intrathecal application of μ-opiate receptor agonists pre-empt development of hyperalgesia and allodynia following inflammation, surgery or nerve injury (Abram and Yaksh, 1993; Abram and Olson, 1994; Brennan et al., 1997; Gonzalez et al., 2000; Kouya and Xu, 2004). Some recent studies on experimental animals showed, however, that opioids may fail to pre-empt hyperalgesia during inflammation or trauma when given systemically (Abram and Olson, 1994) or intrathecally (Brennan et al., 1997).

2.4. Human pain patients

The benefits of opioids for preventing the transition from acute to chronic pain in human patients are not clear (Kelly et al., 2001; McQuay, 1995; see Stubhaug, 2004 for a discussion). In some groups of patients pre-emptive opioids reduced post-surgery pain and consumption of analgesics (Aida et al., 2000b; Katz et al., 2003). In other groups of patients no protective effects were found (Griffin et al., 1997; Motamed et al., 2000). It is obviously of importance for any pre-emptive benefit of opioids that ongoing input from injured or inflamed tissues is adequately dampened, both, in animal (Yashpal et al., 1996) and in clinical studies (Katz et al., 1996). Pre-emptive effects of opioids may also be masked by opioid-induced hyperalgesia (see Ruscheweyh and Sandkühler, 2004 for a discussion). When properly performed the failure or success of pre-emptive opioids might be used as an indicator of the relative contribution of opioid-sensitive mechanisms of central sensitisation to different forms pain chronicity (Collis et al., 1995; Aida et al., 1999, 2000a).

In conclusion, there is clear evidence that opioids are capable of preventing some forms of central sensitisation, both, from pre-clinical and from clinical studies. The general clinical impact is, however, still not well defined. This is caused by lack of understanding of the central mechanisms contributing to allodynia and hyperalgesia, the multitude of effects exerted by opioids and by the scarce number of appropriate clinical trials on the pre-emptive power of opioids.

References


