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Opioids and central sensitisation: I. Pre-emptive analgesia

Jürgen Sandkühler *, Ruth Ruscheweyh

Department of Neurophysiology, Centre for Brain Research, Medical University of Vienna, Spitalgasse 4, A-1090 Vienna, Austria

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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 Sandkühler, 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.

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

* Corresponding author. Tel.: +43 1 4277 628 34/35; fax: +43 1 4277 628 65.
E-mail address: juergen.sandkuehler@meduniwien.ac.at (J. Sandkühler).

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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 (Coull et al., 2003) and/or glycinergic (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 glycinergic 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 allodynia. A small group of neurons has been identified in lamina I of spinal dorsal horn that is necessary for full development of hyperalgesia and allodynia 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 excito-toxicity (Zhang et al., 2000). This is also a potential mechanism of injury-induced cell loss in spinal dorsal horn. It is, however, not know 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

Abram SE, Olson EE. Systemic opioids do not suppress spinal sensitization after subcutaneous formalin in rats. Anesthesiology 1994;80:1114–9.

Abram SE, Yaksh TL. Morphine, but not inhalation anesthesia, blocks post-injury facilitation. The role of preemptive suppression of afferent transmission. Anesthesiology 1993;78:713–21.

Aicher SA, Punnoose A, Goldberg A. mu-Opioid receptors often colocalize with the substance P receptor (NK1) in the trigeminal dorsal horn. J Neurosci 2000;20:4345–54.

Aida S, Baba H, Yamakura T, Taga K, Fukuda S, Shimoji K. The effectiveness of preemptive analgesia varies according to the type of surgery: a randomized, double-blind study. Anesth Analg 1999;89:711–6.

Aida S, Fujihara H, Taga K, Fukuda S, Shimoji K. Involvement of presurgical pain in preemptive analgesia for orthopedic surgery: a randomized double blind study. Pain 2000;84:169–73.

Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology 2000;92:1624–30.

Benrath J, Brechtel C, Martin E, Sandkühler J. Low doses of fentanyl block central sensitization in the rat spinal cord in vivo. Anesthesiology 2004;100:1545–51.

Brennan TJ, Umali EF, Zahn PK. Comparison of pre- versus post-incision administration of intrathecal bupivacaine and intrathecal morphine in a rat model of postoperative pain. Anesthesiology 1997;87:1517–28.

Cervero F, Laird JM. Mechanisms of touch-evoked pain (allodynia): a new model. Pain 1996;68:13–23.

Cervero F, Laird JM, Garci, Nicas E. Secondary hyperalgesia and presynaptic inhibition: an update. Eur J Pain 2003;7:345–51.

Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration. Br J Anaesth 1995;74:396–9.

Coull JA, Boudreau D, Bachand K, Prescott SA, Nault F, Sik A, et al.. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature 2003;424:938–42.

Dickenson AH, Chapman V, Green GM. The pharmacology of excitatory and inhibitory amino acid-mediated events in the transmission and modulation of pain in the spinal cord. Gen Pharmacol 1997;28:633–8.

Gonzalez MI, Field MJ, Bramwell S, McCleary S, Singh L. Ovariohysterectomy in the rat: a model of surgical pain for evaluation of pre-emptive analgesia. Pain 2000;88:79–88.

Griffin MJ, Hughes D, Knaggs A, Donnelly MB, Boylan JF. Late-onset preemptive analgesia associated with preincisional large-dose alfentanil. Anesth Analg 1997;85:1317–21.

Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something. Prog Neurobiol 2000;61:169–203.

Hughes DI, Scott DT, Todd AJ, Riddell JS. Lack of evidence for sprouting of Aβ afferents into the superficial laminas of the spinal cord dorsal horn after nerve section. J Neurosci 2003;23:9491–9.

Ikeda H, Heinke B, Ruscheweyh R, Sandkühler J. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. Science 2003;299:1237–40.

Katz J, Cohen L, Schmid R, Chan VW, Wowk A. Postoperative morphine use and hyperalgesia are reduced by preoperative but not intraoperative epidural analgesia: implications for preemptive analgesia and the prevention of central sensitization. Anesthesiology 2003;98:1449–60.

Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12:50–5.

Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. Can J Anaesth 2001;48:1091–101.

Kohno T, Moore KA, Baba H, Woolf CJ. Peripheral nerve injury alters excitatory synaptic transmission in lamina II of the rat dorsal horn. J Physiol 2003;548:131–8.

Kouya PF, Xu XJ. Buprenorphine reduces central sensitization after repetitive C-fiber stimulation in rats. Neurosci Lett 2004;359:127–9.

Mao J, Sung B, Ji RR, Lim G. Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism. J Neurosci 2002;22:7650–61.

McQuay HJ. Pre-emptive analgesia: a systematic review of clinical studies. Ann Med 1995;27:249–56.

Motamed C, Mazoit X, Ghanouchi K, Guirimand F, Abhay K, Lieutaud T, et al.. Preemptive intravenous morphine-6-glucuronide is ineffective for postoperative pain relief. Anesthesiology 2000;92:355–60.

Müller F, Heinke B, Sandkühler J. Reduction of glycine receptor-mediated miniature inhibitory postsynaptic currents in rat spinal lamina I neurons after peripheral inflammation. Neuroscience 2003;122:799–805.

Ruscheweyh R, Sandkühler J. Opioids and Central Sensitisation: II. Induction and reversal of hyperalgesia. Eur J Pain, in press, doi:10.1016/j.ejpain.2004.05.011.

Nichols ML, Allen BJ, Rogers SD, Ghilardi JR, Honore P, Luger NM, et al.. Transmission of chronic nociception by spinal neurons expressing the substance P receptor. Science 1999;286:1558–61.

Sandkühler J. Learning and memory in pain pathways. Pain 2000;88:113–8.

Sandkühler J, Liu X. Induction of long-term potentiation at spinal synapses by noxious stimulation or nerve injury. Eur J Neurosci 1998;10:2476–80.

Stubhaug A. Can opioids prevent postoperative chronic pain? Eur J Pain 2004 [in press].

Terman GW, Eastman CL, Chavkin C. Mu opiates inhibit long-term potentiation induction in the spinal cord slice. J Neurophysiol 2001;85:485–94.

Willis WD. Long-term potentiation in spinothalamic neurons. Brain Res Brain Res Rev 2002;40:202–14.

Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.

Woolf CJ. Windup and central sensitization are not equivalent. Pain 1996;66:105–8.

Yashpal K, Katz J, Coderre TJ. Effects of preemptive or postinjury intrathecal local anesthesia on persistent nociceptive responses in rats. Confounding influences of peripheral inflammation and the general anesthetic regimen. Anesthesiology 1996;84:1119–28.

Zhang J, Haddad GG, Xia Y. delta-, but not mu- and kappa-, opioid receptor activation protects neocortical neurons from glutamate-induced excitotoxic injury. Brain Res 2000;885:143–53.