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Opioid-induced hyperalgesia

Abstract

Recently it became clear that opioids, besides their role in analgesia, mayalso induce hyperalgesia. Something what in the past was called opioidneurotoxicity. Hyperalgesia, or hypersensitivity to pain stimuli may berelated to well known problems of tolerance to opioids. Hyperalgesia is amajor clinical problem and its recognition and treatment are of paramountimportance. It is believed that uncoupling of opioid receptors from theGi/Go proteins and coupling them to Gs protein changes dramatically activityof opioid receptors. In this article the different aspects of diagnosis andtreatment of hyperalgesia are discussed.

Key words: opioids, hyperalgesia

Introduction

Opioid use has been increasing in recent years. The changing pattern in opioid use has resulted in the emergence of neurotoxicity as a major adverse effect of the treatment of cancer pain [1]. As a consequence, the incidence of neuroexcitatory adverse effects, including hyperalgesia, allodynia, myoclonus, seizures, in patients administered large doses of systemic morphine or its structural analogues to relieve uncontrolled cancer pain, has been increasing in recent years.

The problem of hyperalgesia, tolerance, and nociception remains not clearly understood and quite difficult to interpret in the clinical setting of cancer patients, where multiple factors are able to confound the picture [2]. These conditions are difficult to identify and controversies exist about the real occurrence of this phenomenon in clinical setting [3, 4].

Clinical considerations

Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce abnormally heightened pain sensations, which are characterized by a lowering of the pain threshold, commonly known as hyperalgesia [5]. Such abnormal sensations have been described as being quantitatively different from normal pain sensation and differentially localized from the site of the original pain complaint. This could result in the exacerbation rather than the attenuation of excitatory behaviours.

It is possible to hypothesize an iatrogenic syndrome characterized initially by a declining analgesia, requiring further opioid escalation to maintain the previous level of analgesia — a worsening of pain and whole-body hyperalgesia (panalgesia) often associated with cognitive disturbances, delirium, agitation ranging to screaming in agony, grand mal seizures and multifocal myoclonus. Alternately, patients on opioid therapy, who present long periods of breakthrough nociception due to an inadequate dosage, may require an aggressive treatment with increasing opioid doses. After an initially favourable response, they could develop a hyperexcitated state worsened by further dose increments. The therapeutic difficulties paradoxically stay in accepting the widespread concept of morphine as a pure agonist, with a linear dose-response curve expressed as the more pain, the more drug. Of interest, there are considerable data emphasizing that morphine is not a full agonist, but that it can produce a partial ago-

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nist effect with an increased stimulus [6]. This may correspond to a therapeutic paradox where the consequence (increasing pain), is treated favouring its cause (opioid escalation).

A metabolic explanation has been reported to explain this phenomenon, the ratio of morphine metabolites being altered in favour of inactive, or even antagonistic, morphine-3-glucuronide. Opioids and other neurotoxic agents, including morphine 3 glucuronide, through a non-opioid receptor mediated mechanism, may mimic the antiglycinergic effects of strychnine, although other authors, using a different experimental paradigm, have reported that acute M3G (given in a ratio 4:1) administration increases the acute antinociceptive effects of morphine, presumably by product inhibition of substrate metabolism [7]. The final effect could be dependent on the amount of M3G passing the blood brain barrier. Renal failure may predispose to the syndrome, producing an accumulation of morphine metabolites. On the other hand, all opioid analgesics probably have convulsant activity when administered in sufficiently high doses, as hyperalgesia has been reported to occur even with increasing doses of methadone.

Although much experimental data exist to explain these clinical changes of opioid response, no data exist on how, when and why this occurs, or if it is a simple consequence of a rapid derangement of the central nervous system, possibly occurring in the last days of life. Nevertheless, experimental models provide new information and hypothesis, which may help in understanding some difficult clinical conditions.

Biochemical changes associated with hyperalgesia

In recent years, experimental and clinical studies have pointed out the possible autonomous hyperalgesic effect of high doses of opioids. More recently, it has been recognized that tolerance can develop rapidly from chronic as well as acute opioid exposure. Spinal morphine has been associated with paradoxical algesia and hyperesthesia, which were naloxone-insensitive (8). Similar observations have been reported for hyperalgesia. Rapid development of tolerance and hyperalgesia, normally considered as independent unrelated phenomena, share some common biochemical mechanisms [9], even in acute conditions. Intense opioid receptor activation, such as that occurring with short-lived opioid remifentanyl overdosing, induces rapid and extensive tolerance which has been shown in humans and perhaps manifesting as dramatic hyperalgesia [10].

The development of tolerance and hyperalgesic states involves the activation of excitatory glutamate receptors at the N-methyl-D-aspartate (NMDA) type in the central nervous system. After repeated high intensity noxious stimulation, NMDA receptor activation initiates an intracellular cascade, principally consisting in an increase of intracellular calcium concentration, activation of protein kinase (PKC) and the calcium-calmodulin-mediated production of nitric oxide (NO). Increases in membrane-bound PKC occurring in spinal cord have been shown to positively correlate with the degree of hyperalgesia. The expression of NO-synthases is upregulated after different series of painful stimuli, and NO release contributes to secondary hyperalgesia and allodynia. Being a highly diffusible molecule, NO is believed to be an important messenger in signal transduction pathways that enhance nociceptive transmission in the central nervous system. NO synthase inhibitors can reverse hyperalgesia induced by nerve injury and result in the prevention or retardation of the development of opioid tolerance [7].

On the other hand, a series of studies suggest cross-talk between opioid receptors and NMDA receptors. Opioid receptor activation may result in stimulation of protein kinase C (PKC), an enzyme that phosphorylates several target proteins, including NMDA receptors. Phosphorilation of this receptor results in a release of the Mg++ block, entry of calcium in the cell, and activation of a series of cascades that can lead to opioid receptor down-regulation (opioid tolerance) and hyper-responsiveness (underlying hyperalgesia). The final cascade of this process induces the synthesis of nitrous oxide (NO), moreover, NO "per se" can alter the level of expression of opioid receptors in immunocytes [11]. Alternately, activated glia cells (these also of hematologic origin), could be implicated in the genesis of morphine tolerance, and it has been hypothesized that they could release substances that create situations of exaggerated pain such as allodynia, hyperalgesia, morphine resistance or tolerance [12].

A feature of both nerve-injury pain and opioid-induced hyperalgesia is an increased spinal dynorphin. It has been demonstrated that abnormal pain and decreased opioid antinociception seen after sustained opioid exposure is mediated by spinal dynorphin. Spinal dynorphin content was elevated after opioid infusion, suggesting that opioids can regulate the expression of spinal dynorphin, probably as a result of opioid occupation. The over-expression of spinal dynorphin is also likely to have consequences on the release of excitatory neurotransmitters,

such as substance P. The effects of dynorphin antiserum parallel those seen with NMDA-antagonist MK-801 and suggest that dynorphin may interact, directly or indirectly, with the NMDA receptor [13].

Opioids, opioid antagonists and opioid-induced hyperalgesia

There is a significant variability among opioid drugs in inducing rapid endocytosis of opioid receptors. This is an independent functional property that distinguishes clinically important analgesic drugs such as morphine and methadone. It is associated with functional desensibilization of receptor-mediated signal transduction, which is implicated in the development of tolerance and dependence [14]. Cellular signs of tolerance are due to sustained activation of supersensitized excitatory opioid receptor functions. Activation of Gs-coupled opioid receptors on sensory neurons elicits stimulatory effects via an adenylate cyclase/cyclic AMP/protein kinase A-mediated transduction system, which thereby attenuates inhibitory effects mediated by concomitant activation of Gi/Go-coupled opioid receptors on these cells. Opioid receptors can be rapidly interconverted between inhibitory Gi/Go-coupled and excitatory Gs-coupled modes following alterations in the concentrations of a specific glycolipid, GM1 ganglioside, abundantly distributed on the surface of neuronal cell membranes. This dynamic plasticity provides a cellular mechanism that may underlie modulation of upload analgesia, tolerance, or hyperalgesia [15]. Opioid tolerance is mediated not only by up-regulation of the well known Gs/AC/cAMP/ /PKA second messenger system, but also by elevation of GM1 ganglioside following activation of the cAMP/PKA-dependent glycosyltransferase that synthesize GM1. Elevation of GM1 by sustained activation of Gs-coupled opioid receptor functions may increase the conversion of opioid receptors from the inhibitory to excitatory Gs-coupled mode, resulting in an increased efficacy of coupling of Gs-coupled opioid receptors to the AC/cAMP transducer system, and consequently in supersensitized excitatory opioid receptors.

Recent data have offered further interesting advances in the knowledge of these biochemical processes. A remarkably low concentration of morphine may mediate excitatory Gs-coupled opioid receptor effects, which may provide insights into the mechanisms underlying opioid hyperalgesia, or anti-analgesia. Low concentrations of antagonist opioids have been found to have selective antagonist actions on excitatory, but not inhibitory, opioid receptor-mediated function in dorsal root ganglion neurons. Thus, a direct competitive antagonism of Gs-coupled excitatory opioid receptor functions by co-treatment with extremely low doses of clinically available opioid antagonists, e.g. naloxone markedly enhances morphine's analgesic potency and simultaneously attenuates opioid tolerance and dependence [15]. These observations are in contrast to traditional opioid pharmacology concepts, which fail to acknowledge that morphine or other opioid agonists can activate opioid receptors distributed in both excitatory Gs-coupled as well as inhibitory Gi/Go-coupled modes on nociceptive neurons.

Hyperalgesia as a consequence of inappropriate opioid treatment

Although a continuous exposure to opioids has been recognized to induce analgesic tolerance and abnormal pain, a real opioid-induced hyperalgesia is exceptionally present in opioid addicts. It has been hypothesized that these conditions are dependent on a compensatory neuronal activity consequent to intermittent withdrawal crisis, rather than to opioid escalation *per se* [16]. Thus, the growing evidence of an abnormal response to opioids in cancer patients, where a withdrawal syndrome can be excluded, can be explained, for example, as an inappropriate opioid administration leaving periods of poor pain control (breakthrough analgesia). Inadequate opioid receptor occupancy has been found to produce breakthrough pain, induced by spinal glutamate release, independent of small afferent input, as in neuropathic pain, contributing to an enhanced loss of opioid receptor function [17]. Clinically, this condition may be reproduced with prolonged periods of uncontrolled pain between dose increases.

Hyperalgesia and tumours

The presence of opioid receptors in tumorous cells and the possible opioid trapping mimicking tolerance [18] offer new fascinating insights to explain the response to opioids in cancer patients. Opioid receptor subtypes are expressed in human surgical specimens of both normal and non-small cell lung cancer. The role of opioid receptor in tumour cells could be minimal after receptor saturation, but nitric oxide (NO) release is mediated through these receptors and morphine-stimulated NO release is significantly higher and prolonged than in normal lung [19]. This could create conditions for persistent hyperalgesia.

Methods to counteract opioid-induced hyperalgesia

In escalating opioid doses rapidly recognition of the development of hyperalgesia should be suspected, as higher doses of opioids may stimulate rather than inhibiting the central nervous system, with different mechanisms, well recognized in experimental studies. Alternative procedures should be taken into consideration to break this vicious circle before pain conditions worsen irreversibly.

Opioid switching is increasingly used in patients with a poor opioid response. The presumed offending drug should be stopped, and a rapid opioid substitution should be started [20]. Of concern, while opioid switching often reserves particular cautions, particularly when switching to methadone, the matter is even more complex, in patients who are presenting increasing pain with increasing opioid doses, as antinociception cannot be clearly distinguished from hyperalgesia, and the simple discontinuation of the offending opioid may produce a reduction in pain intensity. Regardless of the different modalities proposed in literature, all these calculations do not take into account the modality of the previous opioid escalation from a dynamic point of view, that is the short time used to increase the dose, or other causes as the driving force for opioid escalation, for example the development of opioid-induced hyperalgesia. Of course, the exact threshold between antinociception and hyperalgesia is un-known and impossible to determine. Thus, starting doses should be lower than expected, even when using an approach of doses inversely proportional to the previous dose. Possibly, a patient controlled analgesia [2], according to the patient's response and careful clinical monitoring, would be an effective and safe alternative, as dosing is clinically mediated in some way, regardless of possible calculations, which are unreliable in such clinical situations.

There are some reports in literature which could be interpreted in the light of more recent knowledge regarding opioid-induced hyperalgesia. At some levels of opioid doses associated with tolerance and hyperalgesia, it is impossible quantify any approximate dose conversion rate. For example it has been reported that only 1% of the equianalgesic dose of the prior opioid, which was parenteral morphine in doses of 21.600 mg/day. Such megadoses of opioids have been the subject of controversy as they could be prevented by using other available methods or route of administration. It is likely that patients receiving grams of parenteral morphine, or any other opioid, may have a prevalent hyperalgesic component, so that the elimination of the first opioid *per se* implicates a consequent reduction of the state of hyperexcitation, to a level of "nociception" attributable to a meaningfully actual painful input, which requires doses even lower than expected with any prudent conversion ratio.

New research areas

In cancer pain treated with opioids, there is discharge of afferent c-fibres, set off by the cancer injury, directly or indirectly, causing a state of central sensitisation. The development of hyperalgesia and the rightward shift of opioid antinociceptive dose-response curve were prevented by the administration of NMDA receptor antagonists. NMDA antagonists do not affect the initial fast synaptic transmission in dorsal horn neurons but selectively inhibit the increase in neural responses to successive stimuli. Thus, ketamine per se produces only a week analgesic effect, but significantly influences central hyperexcitability and inhibits wind-up in dorsal horn neurons. Ketamine has been reported to improve analgesia in patients with uncontrolled pain receiving high doses of opioids administered by different routes. Experimental studies have shown that single doses of a NMDA antagonist may reduce hyperalgesia but not enhance morphine antinociception. Ketamine, a non-competitive NMDA antagonist, has been shown to inhibit wind-up in wide range neurons and to be involved in central temporal summation and central sensitisation. Ketamine may act predominantly by reversing morphine tolerance and/or opioid-induced hyperalgesia, as the blockade of NMDA receptors does not change baseline nociceptive response to painful stimulation or baseline spontaneous pain, and NMDA receptor antagonists per se are unlikely to act as analgesics. They are most likely to reduce the gain of pain intensity rather than removing the normal pain response, although in a clinical setting is quite difficult to differentiate an antihyperalgesic and antinociceptive effect. It has been suggested that intermittently administered ketamine would bring about a more long-term reversal of the central changes [21]. With these experimental observations in mind, a clinical approach with pulse ketamine could be effective in reversing opioid tolerance in patients taking high doses of opioids, who are potentially at risk for future adverse effects.

The use of substances able to reverse hyperalgesia while interrupting this process at the spinal cord

level could also be helpful. Local anaesthetics, used in combination with low doses of opioids intrathecally, are of paramount importance in patients presenting increasing pain with escalating doses of opioids. Other than providing analgesia with a different mechanism, local anaesthetics may offer further advantages. Subtypes of sodium channel are differentially expressed in sensory neurons in the presence of continuous and high intensity discharges from nerve or tissue injury. It has been observed that constant nerve depolarisation increases the potency of local anaesthetic block and could preferentially block certain subtypes of sodium channels involved in injury-induced pathologic depolarization, without affecting the sodium channels involved in normal signalling [22].

In vitro and *in vivo* studies have demonstrated that direct competitive antagonism of Gs-coupled excitatory opioid receptor functions by co-treatment with extremely low doses of naloxone markedly enhances morphine's analgesic potency and simultaneously attenuates opioid tolerance and dependence. Excitation would produce hyperalgesia or tolerance, whereas inhibition would produce typical opioid effects. Anti-hyperalgesic effects have been found even with low receptor concentrations of opioids in a recent experimental bimodal means of opioid receptor activity. This kind of modulation of the action potential of nociceptive neurons appears to be mediated by activation of GM1-regulated interconvertible opioid receptors that can occur either in an inhibitory mode or in an excitatory mode. These modes seems to be induced by higher (mcg) and lower opioid concentrations (pM range), respectively. Selective blockade of excitatory opioid effects in neurons by co-treatment with pM doses of naloxone has been found to attenuate the "anti-analgesic" effects of opioid agonists and thereby enhance their "analgesic" efficacy. The inhibitory mode, leading to inhibitory effects, that is "analgesia", is blocked by relatively high doses of naloxone (nM range) [23].

Conclusions

Although the problem of hyperalgesia, tolerance, and nociception remains not clearly understood and quite difficult to interpret in the clinical setting of cancer patients, where multiple factors are able to confound the picture, the integration of basic knowledge and clinical aspects may help assist clinicians to apply specific alternative approaches in daily activities when such difficult conditions occur.

In escalating opioid doses rapidly recognition of the development of hyperalgesia should be suspected, as higher doses of opioids may stimulate rather than inhibit the central nervous system, with different mechanisms, well recognized in experimental studies. Alternative procedures should be taken into consideration to break this vicious circle before pain conditions worsen irreversibly. More data are needed to detect these conditions early, as actually no diagnostic information on specific markers, clinical or biochemical, exists and most cases are individuated *a posteriori*, given the rapidity of the events in such conditions.

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