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REVIEW ARTICLE

Opioids Resistance in Chronic Pain Management

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Abstract: Chronic pain management represents a serious healthcare problem worldwide. Chronic pain affects approximately 20% of the adult European population and is more frequent in women and older people. Unfortunately, its management in the community remains generally unsatisfactory and rarely under the control of currently available analgesics. Opioids have been used as analgesics for a long history and are among the most used drugs; however, while there is no debate over their short term use for pain management, limited evidence supports their efficacy of long-term treatment for chronic non-cancer pain. Therapy with opioids is hampered by inter-individual variability and serious side effects and some opioids often result ineffective in the treatment of chronic pain and their use is controversial. Accordingly, for a better control of chronic pain a deeper knowledge of the molecular mechanisms underlying resistance to opiates is mandatory.

Keywords: Chronic pain, opiate resistance, polymorphisms.

INTRODUCTION

Chronic pain management is one of the most debated issues in pharmacology and public healthcare. Epidemiological studies show that in Europe one in five adults suffer from chronic pain [1], often of unknown etiology and rarely under the control of currently available analgesics [2]. Opioids have been used as analgesics for a long history and are among the most used drugs [3]. Interestingly, they have been used for centuries for the treatment of pain but their molecular targets were discovered only about forty years ago, in the early $70_{s,}$ when the full blossom of receptor binding studies made it possible [4]. Opioid receptors belong to the family of G-protein coupled receptors and, in particular, they are coupled to pertussis toxin (PTX)-sensitive or PTX-insensitive $G_{i/o}$ proteins. The discovery of the second messenger system coupled to the receptor binding of opioid drugs led to the understanding of their mechanism of action. These receptors mediate an inhibitory signal of neural transmission involved in the analgesic action of opioids. The discovery of opioid receptors prompted the isolation of the first two endogenous opioid neurotransmitters called Met-enkephalin and Leu-enkephalin [5]. Since then, several opioid peptides were identified and the following studies led to a better understanding of their properties [6]. However, while there is no debate over the short term use of opioids for pain management, there is limited evidence to support the efficacy of long-term treatment for chronic non-cancer pain [7, 8] and some of them are often ineffective in the treatment of chronic pain and their use is controversial. This is likely due to the inter-individual variability originating from the presence of several polymorphisms which attract genes involved in the actions of the opioid system. In addition, the use of chronic opioid therapy is limited by a set of problems. These include tolerance, addiction, pseudo-addiction, opioid induced hyperalgesia, bowel dysfunction, suppression of testosterone, cognitive impairment, substance abuse and diversion [9]. In this article we review the literature to draw a comprehensive picture of the mechanisms underlying resistance to opioids for a better control in chronic pain management.

CAUSES OF CHRONIC PAIN

Chronic pain is a multifactorial condition, caused by the complex interplay of several pathogenic mechanisms [10, 11]. This condition can be triggered by lesions or diseases affecting the somatosensory nervous system [12]. Costigan and colleagues described it as an expression of maladaptive plasticity within the nociceptive system [13]. Particularly, several changes, *e.g.*, facilitation and disinhibition of synaptic transmission and neuroimmune interactions, spreaded across the nervous system contribute to dysregulation of pain neurocircuitry and neurochemistry resulting in complex pain phenotypes. Chronic pain is associated with specific and nonspecific medical conditions and generally, it is broadly

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categorised as cancer pain and non-cancer pain [11]. Non-cancer pain can be caused by specific chronic medical conditions such as osteoarthritis, back pain, fibromyalgia, diabetic neuropathy and migraine headaches [11, 14]. However, several pathophysiological situations might also induce it, such as alcoholism [15], HIV/AIDS [16, 17] and neurodegenerative disorders, such as multiple sclerosis [18, 19]. All these diseases have a different impact on the opioid system. For example, several animal and human studies have shown a decreased analgesic potency of μ opioid agonists in diabetic neuropathic pain [20-24]. Chen and Pan reported that the inhibitory effect of systemic morphine on spinothalamic tract neurons is substantially reduced in diabetic rats suggesting a reduction in or dysfunction of opioid receptors in the spinal cord dorsal horn in diabetes [25]. Interestingly, some studies demonstrated a reduction in spinal μ opioid receptors [26, 27] whereas others suggested that the reduced analgesic action of opioid agonists in diabetic neuropathic pain is due, at least in part, to impaired receptor-G protein coupling [28]. Following nerve injury, primary afferents reduce their expression of μ opioid receptors (MOR), and dorsal horn neurons are less sensitive to inhibition by μ opioid agonists [29]. Some authors reported a deficient functioning of MOR at the supraspinal level and k-opioid receptors (KOR) at the spinal level in diabetic mice related to the activation of δ opioid receptors (DOR) at both the supraspinal level and spinal levels [30]. Moreover, the dysfunction of adenosine triphosphate-sensitive potassium channels may contribute to the reduction in MOR-mediated analgesia in diabetic mice [31]. Alcoholism also impacts the opioid system. In fact, prolonged exposure to ethanol can promote an upregulation of functional DOR in the spinal cord and modulate MOR-mediated analgesia [32]. In addition, Hull and colleagues suggested that ethanol may reduce opioid tolerance in mice at the cellular level acting on the γ-aminobutyric acid (GABA)ergic system either at the level of GABA release or GABA receptors [33]. Furthermore, the HIV-1 envelope glycoprotein 120 (gp120) has been shown to increase MOR mRNA expression in human vascular endothelium [34] and also in HL-60 human promyelocytic leukemia cells differentiated into macrophage-like cells by 12-O-tetradecanoylphorbol-13-acetate (TPA) [35]. In addition, more recently, Dever and colleagues reported that the expression of MOR-1 and other MOR variants may be differentially regulated by HIV-1 [36]. Interestingly, the combination of opioids and HIV-1 infection may promote the damage of neurons and glia in the pain-processing neural pathway [17]. Preclinical investigations utilizing animal models, as well as clinical observations with multiple sclerosis patients, also suggested alteration of endogenous opioid systems in the disease. Particularly, Gironi and colleagues found reduced β-endorphin concentrations in peripheral blood mononuclear cells of patients with multiple sclerosis [37]. More recently, in a Theiler's murine encephalomyelitis virus model of multiple sclerosis, Lynch and colleagues reported that mRNA levels of MOR, KOR and DOR are significantly decreased in the spinal cord [38].

LIFE STRESSFUL EVENTS AND CHRONIC PAIN

Several evidences in rodents and humans have highlighted a crucial role of early life stressful events (such as early maternal separation, physical violence, sexual or psychological abuses) in the development and worsening of chronic pain [39-44]. The neurobiological mechanisms underlying the relationship between early-life stress and development of chronic pain are unclear, however, clinical and preclinical data suggested a key role for some neuro-biological substrates, *e.g*. the hypothalamic-pituitary-adrenal axis, neurotransmissions (monoaminergic, opioidergic, endo-cannabinoid) and immune systems [45-47]. In this regard, Interestingly, in maternal separation, one of the most commonly used models of early-life stress, Ploj and colleagues reported altered expression of the endogenous opioids dynorphin and enkephalin in the hypothalamus, substantia nigra, amygdala, and periaqueductal gray key brain areas in the modulation of emotional and nociceptive processes [48]. Moreover, Alexander and colleagues reported that stress potentiates nerve injury-induced tactile allodynia through a mechanism involving glucocorticoids acting at glucocorticoid receptors and glutamate receptor-mediated extracellular signal-regulated kinase (ERK) activation in dorsal horn neurons suggesting that these pathways converge to cause central sensitization [42]. Epigenetic alterations may also represent one of the key mechanisms underlying the development of chronic pain in later life [43, 47, 49-51].

Recently, several data supported a relationship between early life stressful events and increased oxidative stress in the central nervous system (CNS) suggesting a crucial role in the etiopathogenesis of psychiatric disorders such as anxiety, depression, drug abuse or psychosis [52, 53] and also chronic pain [54-57]. Interestingly, some reports have shown that impaired mitochondrial energy production reduced MOR but not DOR or KOR function in neuronal SK-N-SH cells [58, 59]. Moreover, DOR agonists may exert neuroprotective effects on cells [60] and rat brain [61] attenuating intracellular oxidative stress. In particular, Wallace and colleagues demonstrated that δ agonists can act in human SK-N-SH cells in part through a receptor-mediated mechanism [60], whereas Yang and colleagues reported that DOR activation attenuates oxidative injury in the ischemic brain by enhancing the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase and reduces free radicals, malondialdehyde and nitric oxide (NO) [61]. More recently, Chao and colleagues, reported that DOR activation may exert neuroprotective effects against hypoxic/ischemic Na+ influx through Na+ channels *via* a protein kinase C (PKC)-dependent pathway in the cortex [62]. Xe and colleagues also suggested that DOR signaling could act at multiple levels to confer neuronal tolerance to harmful insult [63].

PAIN: PHARMACOLOGY AND CLINIC USE OF OPIOID DRUGS

The control of pain is the most used therapeutic action of opioids. Opioids are commonly prescribed because they are effective in relieving many types of pain. At the moment, opioids represent the most effective treatment for chronic cancer pain conditions [64]. Moreover, in these years, despite limited strong scientific evidences, use of opioids for chronic non-cancer pain has increased remarkably [8, 65]. However, the use of opioids in pain management requires careful dose escalation and empirical adjustments based on

clinical response and the presence of side effects or adverse drug reactions. The forefather of opioid analgesics, that still remains the most used drug in the management of chronic pain conditions, is morphine. Morphine is extracted from opium obtained through *Papaver somniferum* because it accounts for 10% of the alkaloids contained in this latex. The first firm reference to opium employment is traceable in Teofrasto's writings dating back to the third century b.C. [66]. The pioneer study of Snyder and his colleagues led in the 1970s to identify high affinity binding sites for opioids in intestine and brain [4]. Opioid receptors belong to the large superfamily of seven transmembrane spanning G protein-coupled receptors and are classified as μ (μ_1, μ_2, μ_3), δ (δ_1, δ_2), k (k_1, k_2, k_3) and ORL1 [67]. These receptors have been cloned and their $cDNA_s$ described in the years from 1992 to 1994 demonstrating that their corresponding mRNAs present more than 60%-homology [68]. Opioid receptors activation inhibits adenylate cyclase (AC)-cyclic adenosine 3',5'-monophosphate (cAMP) – protein kinase-A (PKA) signal transduction pathway thus modulating a wide series of effectors up to mitogen-activated protein kinase (MAPK) family [69, 70]. For a long time it has been thought that opioid receptors could be coupled only to PTX-sensitive Gi/o proteins but, after several studies, it was demonstrated that all of these receptors can transduce their signal even through the PTX-insensitive subunits Gz, G14 and G16 which also stimulate G protein-coupled inwardly rectifying K+ channel (GIRK) and inhibit AC [71, 72]. Inhibition of the signal transduction of the pathway AC-cAMP-PKA by opioid receptors activation leads to reduced neuronal excitability and consequently nociceptive stimuli transmission. It was demonstrated that opioid receptors were particularly expressed in pain-modulating descending pathways, which include the medulla, *locus coeruleus*, medial thalamus and periaqueductal gray area. They were also expressed in limbic, midbrain, cortical structures and in the spinal cord *substantia gelatinosa* [73]. Pain stimuli are perceived by nociceptors and are inserted at level of the dorsal horn of spinal cord [74]. At this point opioid drugs come into action because the cells of the *substantia gelatinosa* are inhibitory interneurons rich of opioid receptors that are activated by the antinociceptive descending system and regulate painful stimuli transmission from primary afferents to spino-thalamic neurons. Characterization of the properties of opioid receptors sharpened the interest for identifying endogenous opioid-like neurotransmitters. In 1975 Hughes and Kosterlitz isolated two pentapeptides endowed with high affinity for opioid receptors, *i.e*. Met-enkephalin and Leu-enkephalin [5]. Additional opioid peptides were successively isolated and classified as enkephalins, endorphins, dynorphins and endomorphins according to their structure [73]. Several other non-mammalian opioid peptides, which show affinity to opioid receptors, have been discovered to date. These include opioid peptides derived from amphibian skin [75], opioid peptides derived from plant proteins [76] and opioid receptor ligands derived from food proteins [77]. Today, opioids can be classified in different groups comprehending morphine analogues, thebaine analogues, phenylpiperidines, methadone analogues and benzomorphanes [78]. In the class of morphine analogues we can recognize heroin, codeine, nalorphine, naloxone, naltrexone *etc*. The baine analogues, like buprenorphine, are synthetic derivatives of which the chemical structure is unrelated to morphine. Among phenylpiperidines we can find fentanyl and the methadone analogues (*e.g*. dextropropoxyphene). The main representatives of the class of benzomorphanes are pentazocine and cyclazocine. For what concerns the pharmacodynamic of opioids, they are distinguished in agonists (morphine, codeine, meperidine, methadone, tramadol, tapentadol, fentanyl, oxycodone), partial agonists (buprenorphine), mixed agonist-antagonsts (pentazocine) and antagonists (naloxone, naltrexone). For the clinical use the most employed drugs are tramadol, codeine and oxycodone (often in combination therapy with paracetamol), that are classified as mild opioids, and morphine and fentanyl categorized as strong opioids. Opioids are strong or mild according to the pain conditions in which they are used [79, 80]. Tramadol is a synthetic analogue of codeine very useful both in the treatment of nociceptive chronic pain and in neuropathic pain syndromes [81], in which it represents a second line therapy when gabapentin, pregabalin or tryciclic antidepressants seem not to work anymore. It is very interesting to know that this drug is sold in the shape of racemic mixture since this is more effective than the single enantiomers. It is well known that in this mixture (+) enantiomer binds μ receptor and inhibits serotonin reuptake, while (-) enantiomer inhibits noradrenaline uptake and stimulates α_2-adrenergic receptors [82]. Tramadol has a better potency ratio relative to morphine in neuropathic pain than in nociceptive pain models suggesting that this increase in potency of tramadol is likely due to its monoaminergic mechanism [83]. Tapentadol is a novel MOR agonist whose activity is several-fold greater than tramadol, with prominent norepinephrine reuptake inhibition (NRI) and minimal serotonin effect [84]. Tapentadol showed antinociceptive and antihyperalgesic activity in various models of acute and chronic inflammatory pain, and both MOR agonism and NRI were found to contribute to these effects [85]. In addition, tapentadol has the benefit of greater gastrointestinal tolerability compared to classical strong opioids. Codeine, a mild μ opioid agonist, has gained much popularity as a single agent or in combination with a non-opioid agent, such as paracetamol, for the treatment of mild to moderate pain. Codeine has a very low affinity for opioid receptors and its analgesic effect is dependent on its conversion to morphine through the cytochrome P-450 enzyme 2D6, enzyme highly polymorphic (see below) and responsible of variability in inter-individual response to this opioid [86]. Oxycodone is a semisynthetic opioid analgesic derived from thebaine that acts at MOR and KOR. Oxycodone has a high oral bioavailability and produces more predictable plasma concentrations than morphine [87]. The clinical efficacy of oxycodone is similar to that of morphine and it, alone and in combination with paracetamol, is a useful opioid analgesic in acute postoperative pain, cancer pain, visceral pain and chronic nonmalignant pain [88]. Oxycodone combined with a μ receptor antagonist may improve pain control, reduce physical tolerance and withdrawal, minimizing opioid-related bowel dysfunction and act as an abuse deterrent [89]. Morphine and fentanyl have strong agonist activity for μ receptors and they bind more selectively these opioid receptors compared to the others. Morphine is commonly used as a reference for all other opioids. Its main

indications of use are for postoperative and chronic malignant pain, however, it is also used for other severe pain conditions (*e.g*. colic pain, angina pectoris) [90]. Fentanyl is a potent synthetic μ-opioid receptor agonist with a rapid onset and short duration of action [91]. This compound is 75-125 times more active than morphine [92] and is extensively used for anesthesia and analgesia in intensive care units in combination with propofol and midazolam [93]. At present, fentanyl is the only rapid-onset analgesic that is suitable for the treatment of breakthrough pain [91]. The pure agonists have no apparent ceiling effect for analgesia, however, meperidine is associated with excitatory side effects with a risk of seizures and it is not recommended for the treatment of chronic pain [81]. Partial agonists with mixed agonist-antagonist action are generally not indicated for the treatment of chronic pain [94], however, in 2011 the Food and Drug Administration has approved a transdermal formulation of buprenorphine for treatment of moderate to severe chronic pain [86]. Interestingly, buprenorphine may also act as a potent local anesthetic and blocks voltage-gated sodium channels *via* the local anesthetic binding site [95] and this property is likely to be relevant when buprenorphine is used for pain treatment and for local anesthesia. Ideally, the greatest analgesic activity would be obtained by a drug able to activate μ receptors and to inhibit k receptors. Activation of μ receptors present on GABA-ergic interneurons in the nucleus of the *raphe magnus* reduces GABA release, removing the inhibition of the primary neurons that give origin to the discendent pathway inhibiting painful stimuli transmission at spinal level. On the contrary, k receptors localized on primary neurons of the nucleus of the *raphe magnus* cause hyperpolarization and consequent blockade of the inhibitory descending pathway. Opioid receptors may interact with each other to form heteromeric complexes and these interactions affect morphine signaling [96, 97]. Since chronic morphine administration leads to an enhanced level of these heteromers, these opioid receptor heteromeric complexes represent novel therapeutic targets for the treatment of pain and opioid addiction [98]. At the cellular level, opioid receptors are inhibitory and prevent the presynaptic release of a number of neurotransmitters. Of particular interest were the observations that opioids inhibited the release of glutamate, calcitonin gene related protein (CGRP), and substance P in view of their established roles in pain circuitry and nociceptive transmission [99]. Glutamate has a unique place in nociception since activation of N-methyl-aspartate (NMDA) receptors has been associated with centrally mediated chronic neuropathic pain and hyperalgesia and 'wind up', which is induced by sustained depolarization of wide dynamic range (WDR) neurons found in deeper layers of the dorsal horn [100]. Substance P is known to contribute to chronic inflammatory pain and participate in central sensitization and associated hyperalgesia [101-103]. CGRP is released from primary afferents and facilitates the activity of substance P within the dorsal horn [100]. Recently, in *in vivo* experiments, Endres-Becker and colleagues [104] found that locally applied morphine reduced capsaicin-induced thermal allodynia, suggesting that MOR activation can also inhibit the activity of the transient receptor potential vanilloid type 1 (TRPV1) *via* G(i/o) proteins and the cAMP pathway. Opioids show a wealth of side effects, among which one of the most dangerous is respiratory depression due to a reduction of sensitivity of the brainstem respiratory centers to CO_2 tension. Moreover, these drugs depress pontine and bulbar centers involved in the modulation of the respiratory rhythm [105]. Other side effects are constipation, vomiting, myosis, cough reflex suppression and modulation of the immune system. In particular, opioids have the capability to modulate immune system both through direct effects on immune cells and *via* indirect effects mediated by central neuronal mechanisms [106]. However, it has been suggested that not all the opioids affect immune function in the same way [107] in particular, morphine and tramadol at analgesic doses induce different effects on immune system [108]. A repeated or prolonged use of opioids causes adaptive modifications that lead to tolerance, craving and addiction [109]. These adaptive modifications range from the receptors modulation and uncoupling with G protein to the hyper-activation of the cAMP-pathway, and so of the AC, with consequent increase of the proteins CREB (cAMP response element-binding protein) and fos. Hyperactivation of AC is encountered in tolerance and addiction [81]. One of the future challenges in this field is to obtain non-addictive opioids. To pursue this purpose, Mizoguchi and colleagues [110] synthesized compounds like amidino-TAPA. This drug probably exerts its pharmacologic action *via* the release of endogenous k opioid peptides and appears to be non-addictive and more effective on neuropathic pain [111].

OPIOIDS RESPONSIVENESS IN NEUROPATHIC PAIN

Neuropathic pain is a clinical manifestation characterized by the presence of allodynia and hyperalgesia, and it is difficult to treat with the most potent analgesic compounds [112]. Since the fundamental pathophysiologic mechanisms of neuropathic pain remain unclear, the exact mechanisms which may account for the weak efficacy of opioids in certain neuropathic pain states remain elusive [80, 113]. It has been suggested that this reduced opioid responsiveness may be related to inter-individual variability (see below) but also to multiple factors including desensitization of opioid receptors [114], functional changes in glutamate receptors [115] and transporters [116] and uncoupling of G-protein from opioid receptors [117]. β-arrestin has been also demonstrated as playing an important role in regulating opioid receptors [118, 119]. It has been suggested that reduced opioid responsiveness may be related to the lack of supraspinal/spinal synergy that is normally associated with morphine efficacy in conditions of acute pain determining a disturbance of normal opioid mechanisms/signaling in the spinal cord [120, 121]. In fact, the analgesic efficacy of opioids is significantly reduced from an intrathecal opioid injection compared with an intraperitoneal opioid injection for neuropathic pain states [122, 123]. Particularly, the failure of intrathecal opioids to produce antiallodynic effects may be due, in part, to the lack of available functional spinal opioid μ-receptors which may occur following nerve injury. A reorganization of MORs in the dorsal horn spinal cord follow peripheral axotomy and the reduced effectiveness of opioids may be related to a crucial functional change involving downregulation or desensitization of μ-opioid receptors. Functional downregulation and/or desensitization of these

receptors in the dorsal horn of the spinal cord and particularly in *laminae* I and II has been observed in nerve-injury neuropathy [121, 124] and diabetic neuropathy [125, 126]. The reduced analgesic effect of intrathecal morphine in diabetes is probably due to impairment of μ-opioid receptor-G protein coupling rather than reduction in μ-opioid receptor number in the spinal cord dorsal horn and may be related to increased production of PKC [127, 128]. Neuroadaptation of MOR in the brain may also contribute to the reduced efficacy of opioids in neuropathic pain [129]. A reducing μ-opioid receptor-mediated G-protein activity has been demonstrated in a model of neuropathic pain in the thalamic region of mice [130] and impairment of G transducer proteins Gi2α, Gi3α, and Gzα function led to weaker analgesic responses to various opioids (*e.g.*, methadone, buprenorphine) [131]. Opioid receptor heterodimerization may be an additional contributing factor to clinical variability of opioids. In fact, opioid receptor dimerization can alter opioid receptor selectivity and trafficking [132]. Heterodimers may have different opioid binding profiles compared with monomers, as shown by the association of DORs-1 and KORs-1 [132, 133] to form a receptor consistent with the KORs-2 first proposed from binding assays [134]. Perhaps the most prominent change in ligand selectivity within the opioid field is the dimerization of MORs and the orphanin FQ receptor, ORL-1 [135]. OFQ/N binds to its own receptor with very high affinity and is insensitive to traditional opioids. Coexpression of opioid receptors has been shown to alter opioid ligand properties and affect receptor signaling in cell culture model systems [97, 132, 136-138] and these differences are hypothesized to occur as a consequence of receptor heteromerization.

Sustained agonist activation of MOR initiates rapid regulatory events, including receptor desensitization and trafficking, that are thought to contribute to the behavioral opioid tolerance that develops during prolonged opioid administration [139]. β-arrestins, including β-arrestin 1 and β-arrestin 2, are predominantly expressed in neuronal tissues and regulate G-protein-coupled receptor coupling and signaling [140]. In β-arrestin 2 knockout mice, the tolerance to the antinociceptive effects was significantly attenuated in the tail-flick test [119]. The capacity of opioids to alleviate inflammatory pain is also negatively regulated by the glutamate-binding NMDA receptor (R) [141]. μ-opioid receptors and NMDAR NR1 subunits are associated in the postsynaptic structures of PAG neurons and MOR desensitization secondary to neuropathic pain appears to involve PKA. Therefore, PKA may be responsible for the dissociation of NR1 subunits from MORs, which occurs as a result of NMDAR activation leading to MOR Ser phosphorylation and uncoupling from G-proteins [141]. NMDA receptor and PKC translocation are importantly involved in neuropathic pain and morphine tolerance [142]. In fact, the development of the hyperalgesia and allodynia in neuropathic pain states is suppressed by administration of NMDAR antagonists or PKC inhibitors [110, 143, 144]. The development of morphine analgesic tolerance by increased NMDA receptor activity seems to occur *via* neural nitric oxide synthase (nNOS) [145]. On the other hand, several studies have shown that NO mediates numerous neuropathic pain symptoms [146] and modulates the peripheral antinociceptive effects induced by certain drugs during inflammatory pain, including opioids [147-149]. NO also regulates the transcription of μ- and k-opioid receptor genes under basal and inflammatory conditions [150, 151]. In the brain, morphine increases the production of NO *via* the PI3K/Akt/nNOS pathway [152]. Subsequently, NO enhances NMDAR/calmodulin-dependent protein kinase II (CaMKII) cascade, promotes MOR phosphorylation and its uncoupling from regulated G-proteins [141, 145] diminishing the strength of morphine-activated μ-opioid receptor signaling. An increase in dynorphin A has also been suggested to be involved in the diminished opioid responsiveness that may be seen in neuropathic pain states [153]. Despite dynorphin A is an endogenous opioid with activity at k-opioid receptors [154], many of its effects are blocked by MK-801 but not naloxone, implicating direct or indirect interaction with NMDAR [155]. Neuropathic pain may also inhibit endogenous analgesia in PAG through an increase in presynaptic GABA release [156].

The evidence of increased rates of opioid tolerance development in neuropathic pain states has been examined and found to involve an opioid-induced increase in central immune signaling [157-160]. Opioid exposure induces profound short- and long-term modulations of central immune signaling and recently, it has been suggested that the activation of glial cells, including astrocytes and microglia, at the level of the spinal cord plays an important role in the development of opioid tolerance [160-163]. The opposition of opioid analgesia by acute central immune signaling seems started, at least in part, by an opioid-induced toll-like receptor 4 (TLR4) response. TLR4 knockout mice exhibit a three-fold leftward shift in the systemic dose of morphine necessary for analgesia when compared with wild-type mice [164]. The hypothesis of opioid-induced TLR4 signaling is further supported by the potentiation of acute morphine analgesia after blockade of TLR4 activity [165, 166]. However, recent findings suggest that microglial activation in the development of morphine tolerance is not mediated by TLR4 [167]. The activation of microglia and astrocytes by repeated morphine administration also increased TNFα, IL-1β and IL-6 expression in the spinal cord [168, 169]. Particularly, IL-1β (by intrathecal administration) produces mechanical and thermal hyperalgesia [170, 171] and has been shown to oppose opioid-induced analgesia [172], decreasing morphine efficacy and contributing to the development of morphine tolerance.

Pharmacogenetic of Opioids

The individual variability of opioid pharmacology suggests that the patients' genetic disposition influences the response to opioids. Several studies suggest a genetic variability between individuals and in their ability to metabolize and respond to drugs [113]. Some drug-metabolizing enzymes and transporters (including cytochrome P450 [CYP], uridine 5′-diphosphate [UDP]-glucuronosyltransferases [UGT], and adenosine triphosphate (ATP)-binding cassette [ABC] transporters) may play a significant role in opioid metabolism and affect inter-individual differences in opioid concentrations in the human body and brain. For example, codeine is converted in morphine through a particular isoform of the

cytochrome P450, the CYP2D6 that is involved in the metabolism of several drugs. A well characterized genetic polymorphism of CYP2D6, that affects at least 10% of caucasic population, leads to the incapability to carry out this conversion and so makes codeine ineffective [173]. Chinese population is also less sensitive to codeine. Moreover, in this population even morphine is less effective, likely because of a decreased production of morphine-6-glucuronide [174]. On the other end of the spectrum, those with gene variants resulting in extra copies of CYP2D6 may metabolize codeine to morphine more rapidly and completely than others [175]. Tramadol undergoes metabolism by CYP2D6 to an active metabolite (*O*-desmethyl tramadol), which has greater affinity for the μ-opioid receptor than the parent compound [176]. The modulation of CYP2D6 also affects oxycodone pharmacodynamics [177]. In addition to CYP2D6, CYP2B6, 2C19, 3A4, and 3A5 isoforms are involved in opioids metabolism.

The CYP2B6 gene is highly polymorphic, with at least 50 allelic variants identified [178] and its polymorphism influence the plasma concentration and clearance of the methadone S-enantiomer [179]. CYP3A4 polymorphism is related to the pharmacokinetics of fentanyl and patients with CYP3A4*1G variant A allele have a lower metabolic rate of drug [180]. In Japanese patients with CYP3A5*3 polimorphism the plasma disposition of noroxycodone is altered [181]. In addition, multiple single nucleotide polymorphisms in the promoter region of uridine diphosphateglucuronosyl transferase 2B7 (UGT2B7), the predominant enzyme that catalyzes morphine glucuronidation, have been reported [182]. Presence of the UGT2B7-840G allele is associated with significantly reduced glucuronidation of morphine and thus contributes to the variability in hepatic clearance of morphine in sickle cell disease [183]. The efficacy of opioids in humans may be affected by allelic variants in the genes of transporters, structural proteins that can influence the absorption, distribution, and elimination of opioids [184]. The most characterized of the ATP binding cassette (ABC) superfamily of efflux transporters is *ABCB1* encoding P-glycoprotein. Opioid induced analgesia is increased and prolonged in mice lacking P-glycoprotein [185]. P-glycoprotein can limit the concentration of pain management drugs, such as morphine, in the brain because it actively pumps drugs out of the CNS. Also methadone, loperamide, and fentanyl have all been confirmed as P-glycoprotein substrates [186-188]. *ABCB1* gene is highly polymorphic. The most investigated *ABCB1* genetic polymorphism is the non-synonymous exon 26 SNP, C3435T, which is observed with a frequency of 50-60% in Caucasians, 40-50% in Asians, and 10-30% in Africans [189, 190]. Genetic variation in the multidrug-resistance gene MDR-1 (which encodes for P-glycoprotein), may account for the genetic variability in P-glycoprotein activity [191]. However, about opioids there are not the only genetic variations of the metabolic system to take into account. For example, A118G single nucleotide polymorphism (SNP) in exon 1 of the μ-opioid receptor gene (OPRM1) has been linked to the variability of the analgesic effect of morphine. Individuals with G118 polymorphism have a reduced or variable response to morphine and increased opioid dose requirements during opioid therapy [192]. The SNPs interesting OPRM1 underlie the expression of μ-opioid receptors variants in humans. In particular, A118G SNP causes an asparagine to an aspartate substitution in the extracellular domain of the μ-opioid receptor. This allele has a frequency from 4% to 48% according to the population [193]. Recent studies suggest that this amino acid substitution causes a different capability of the receptor to inhibit native $Ca_v2.2$ calcium currents with a consequent difference in pain perception. It seems that patients endowed with the mutated μ-opioid receptor containing the aspartate show higher sensitivity to the analgesic action due to this receptor activation [194]. A118G SNP has been associated with elevated pain responses and decreased pain threshold in a variety of populations and it seems that A118G genotypes may influence migraine-associated head pain in females [195]. It has also been shown that this polymorphism A118G could be a clinical marker of the outcome of the progression of pain intensity and disability in patients affected by sciatic pain after lumbar disc herniation, since it seems to increase pain stimuli sensitivity in female patients and to protect male patients in the first year following to herniation [196].

In human studies, low catechol-O-methyltransferase (COMT) activity has been associated with increased sensitivity to acute clinical preoperative or postoperative pain [197]. As a result, genetic variability in the COMT gene can contribute to differences in pain sensitivity and response to analgesics. Low COMT activity also increases opioid receptors and enhances opioid analgesia and adverse effects in some cancer [198, 199]. Environmental and/or genetic influences that alter central immune signaling may also contribute to altered acute opioid analgesia. For example, single-nucleotide polymorphisms in the genes encoding IL-6 [200] or IL-1ra [201], which are associated with increased proinflammation, lead to increased opioid requirements after surgery, suggesting a possibly reduced opioid analgesic efficacy combined with or separate from increased pain.

CONCLUSION

Actually, some of the most powerful analgesics belong to the opioid drugs family which is, thus, object of intense study. Opioid receptors field is remarkable among the other fields in pharmacology because of the fact that the earliest findings, made without the aid of the modern molecular biology tools, still remain irrecusable, both about receptors and about endogenous opioid peptides, and the opioid binding sites identified in the 1973 are responsible for the main pharmacological actions of the most clinically used opioids [68]. It remains to clarify the mechanisms of addiction in order to develop non-addictive opioids and to dissect more and more the pharmacogenetic of the opioid system to obtain always the best clinical outcome with opioids therapy. In this way, through translational pharmacology, we would be able to use better the opioid drugs already available and to produce new drugs more effective in pain control and less addictive. The achievement of opioid drugs really active even in neuropathic pain syndromes is a very interesting topic. Indeed, neuropathic pain control is a so debated question that in recent years great effort has been put in understanding the mechanisms of spinal cord synaptic

plasticity which may contribute to neuropathic pain [202]. In fact, it is now clear that pain shares a lot of similarities with other neurobiological processes such as learning and memory [203] and the participation of cellular and molecular mechanisms typical of conditions in which these processes are altered, *i.e*. in neurodegenerative diseases, seems to play an important role in the development and maintenance of pain states. In this regard, autophagy, a major intracellular degradation pathway lately implicated in several pathological conditions and brain diseases [204], represents a novel pathway regulating neuroinflammation and neuropathic pain [205, 206] thus offering a new target for the development of more effective treatments and that could help us understand the different sensitivity to opioids in some pain states.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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