Mechanisms of Opioid-Induced Tolerance and Hyperalgesia

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ABSTRACT:

Opioid tolerance and opioid-induced hyperalgesia are conditions that negatively affect pain management. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in a decrease of the drug’s effects over time. Opioid-induced hyperalgesia occurs when prolonged administration of opioids results in a paradoxic increase in atypical pain that appears to be unrelated to the original nociceptive stimulus. Complex intracellular neural mechanisms, including opioid receptor desensitization and down-regulation, are believed to be major mechanisms underlying opioid tolerance. Pain facilitatory mechanisms in the central nervous system are known to contribute to opioid-induced hyperalgesia. Recent research indicates that there may be overlap in the two conditions. This article reviews known and hypothesized pathophysiologic mechanisms surrounding these phenomena and the clinical implications for pain management nurses.

Opioid analgesics continue to be the mainstay of pharmacologic treatment of moderate to severe pain. Many patients, particularly those with advanced cancer, require chronic high-dose opioid therapy. Achieving clinical efficacy and tolerability of such treatment regimens is sometimes hindered by two opioid-related phenomena. The first is tolerance, which is manifested clinically by the need for increasing opioid dosages over time to maintain the same level of pain relief; this increased need is not explained by disease progression. A second problem that arises is the more recently recognized phenomenon of opioid-induced hyperalgesia (Sjogren et al., 1998). In this situation, prolonged administration of opioids results in a paradoxic increase in atypical pain that appears to be unrelated to the original nociceptive stimulus.

Opioid-induced tolerance and hyperalgesia have been documented in both animal and human studies. They can develop after administration of several types of opioids delivered via various routes, doses (i.e., ultra-low through high dosages), and administration schedules (i.e., intermittent vs. continuous) (Angst & Clark, 2006; Mao, 2006; Ossipov et al., 2005). Cellular changes associated with these phenomena have been identified at many anatomic sites, including afferent neurons, the spinal cord, brain, and the descending modulatory pathway (Gardell et al., 2006; King et al., 2005; Mao et al., 2002; Ossipov et al., 2005; Terman et al., 2004).
Significant clinical challenges arise from opioid-induced tolerance and hyperalgesia. More effective pain treatment can be achieved when these conditions are recognized and managed. Although the mechanisms underlying opioid-induced tolerance and hyperalgesia are not completely understood, research has begun to reveal some of the complex factors that are associated with these phenomena. The purpose of the present article is to describe both the established and the hypothesized mechanisms underlying opioid-induced tolerance and hyperalgesia. The clinical implications of these mechanisms and their possible prevention and treatment also are discussed.

OPIOID RECEPTOR PHYSIOLOGY

A discussion of opioid tolerance is best prefaced with a review of opioid receptor physiology. Researchers have identified three types of opioid receptors: mu, delta, and kappa receptors. These receptors are distributed in various locations within the spinal cord and brain structures. Figure 1 shows the distribution of opioid receptors in the brain of a guinea pig. Mu opioid receptors are highly concentrated in the outer laminae of the dorsal horn of the spinal cord, whereas delta opioid receptors are diffusely distributed throughout the dorsal horn (Quirion, 1984; Quirion et al., 1983). Kappa opioid receptors are concentrated in the outer laminae of the dorsal horn of the lumbar sacral cord and are closely associated with neural input from the visceral structures (Quirion, 1984; Quirion et al., 1983). Two areas of the brainstem—the rostral ventromedial medulla (RVM) and the periaqueductal gray (PAG)—express high levels of mu opioid receptors; delta and kappa receptors are also expressed, albeit at much lower levels (Mansour et al., 1987; Mansour et al., 1995). Studies have demonstrated mu and some delta opioid receptors on neurons that arise from the PAG or RVM and descend to the spinal cord where they inhibit pain transmission (Van Bockstaele et al., 1996).

Clinically available and experimental opioids have differing potency and efficacy at the various opioid receptors. The overall action of a particular opioid is the sum effect of activation of all the relevant receptors. Most of the opioids that are currently used in clinical practice are predominantly mu agonists (although some also bind at delta or kappa receptors or both). There are at least seven “subtypes” of the mu receptor (Pasternak, 2001), and each opioid may have different affinities for the various mu receptor subtypes. Tolerance may develop separately at each mu receptor subtype in response to a particular opioid. When a patient is switched from one opioid to another, the “new” opioid may have a different selectivity for the individual mu receptor subtypes, which explains “incomplete” cross-tolerance and offers a way to overcome tolerance.

This difference in how opioids interact with the mu receptor subtypes and/or their ability to activate the other opioid receptor types could explain or predict clinical differences in the pharmacologic effect of one opioid compared with another. Moulin et al. (1988) studied tolerance in morphine versus levorphanol, an opioid that is active at all three opioid receptors. Pretreatment with levorphanol in rats caused tolerance to morphine and levorphanol, but pretreatment with morphine caused tolerance only to morphine and not to levorphanol, indicating that receptor selectivity influences tolerance (Moulin et al., 1988). More recently, investigators have postulated that the ability of methadone to differentially activate delta opioid receptors may be a contributing factor to its incomplete cross-tolerance in patients who had become tolerant to mu opioids such as morphine (Lynch, 2005).

Some investigators have postulated that genetic variations in receptors, often referred to as genetic polymorphism, can account for interindividually differences in pain sensitivity, opioid analgesic response, and risk of psychologic dependence (Bond et al., 1998; Estfan et al., 2005; Thomsen et al., 1999). Approximately 500 genes have been identified that influence pain in animal and human studies, with about 100
variations in the human mu opioid receptor gene alone (Ross et al., 2006). At present, the functional significance of many of these pain-related and opioid receptor genetic variants has not been fully elucidated. For example, the A118G genetic variant of the mu opioid receptor, which results in a change in amino acids from asparagine to aspartate at position 40, has been studied in both pain (Hirotu et al., 2003; Lotsch et al., 2002; Lotsch et al., 2002; Ross et al., 2005) and addiction (Bergen et al., 1997; Bond et al., 1998; Li et al., 2000; Sander et al., 1998; Town et al., 1999), with conflicting reports on its relationship to morphine potency or its association with risk of substance abuse. A recent study explored the influence of variations in genes that encode the mu opioid receptor and its regulatory proteins on opioid response in a cancer patient population. There were no significant differences in the frequency of several variants of mu opioid receptor genes between patients responsive to morphine and those intolerant of morphine. There were, however, significant differences in frequency of two genetic variants (i.e., stat6, mu opioid gene transcriptional factor; and β-arrestin2, intracellular regulatory protein) between patients who required a switch from morphine to an alternative opioid compared with those who obtained adequate analgesia with morphine (Ross et al., 2005). These differences suggest that genetic variations among individuals influence clinical responses to morphine and possibly other opioids.

**OPIOID TOLERANCE**

Opioid-induced tolerance is described in the simplest pharmacologic terms as a shift to the right in the dose-response curve; in other words, a higher dose is required over time to maintain the same level of analgesia. At times, progressive disease is the reason for higher opioid requirements (Collin et al., 1993; Foley, 1993). Other causes of increased opioid needs are pharmacokinetic or pharmacodynamic changes. Pharmacokinetic changes occur, for example, if the drug up-regulates the activity of a metabolic process that represents a major pathway for its elimination from the body. Enzyme induction results in a gradual reduction in plasma drug concentration while the daily opioid dose remains unchanged. Pharmacodynamic tolerance occurs when a decline in drug effect cannot be attributed to pharmacokinetic factors but instead reflects drug-activated changes in the response of the neural systems. For our purposes, “opioid tolerance” refers to pharmacodynamic tolerance.

Two major theories of opioid tolerance involve changes in opioid receptors. One theory purports that receptors undergo changes that result in decreased receptor activation, or desensitization, with prolonged exposure to opioids. The other line of evidence suggests that opioid receptor down-regulation is at least partially responsible for the development of tolerance.

The desensitization mechanism involves changes in the physiology of the opioid receptors. These receptors belong to the family of G protein–coupled receptors (GPCRs). When the opioid is bound to the receptor, the associated G protein becomes “activated.” Activation of G proteins eventually leads to decreasing excitability along the cell membranes of neurons in the pain pathways. This action occurs through a reduction in cyclic adenosine monophosphate (cAMP), leading to a suppression of Na+ and Ca+ channels and resulting in analgesia (Figure 2). Over time, alterations in the G protein-mediated mechanism can lead to decreased analgesia through opioid receptor desensitization (Ferguson et al., 1998; Luttrell & Lefkowitz, 2002; Perry & Lefkowitz, 2002; Rachal & Bohn, 2005; Shen & Crain, 1990; Terman et al., 2004; Wang et al., 2005; Yoburn et al., 2003). In animal models, this desensitization occurs when intracellular regulatory proteins or enzymes, such as GPCR kinases, β-arrestins, and adenylyl cyclase, are activated by opioids in such a way that they “decouple” the opioid receptor from the G protein or produce a “switch” in coupling of the receptor to a “nonanalgesic” G protein, subsequently decreasing analgesic activity. Receptor desensitization has been previously associated with morphine tolerance in rats (Noble & Cox, 1996; Sim et al., 1996), but more recent reviews underscore how much is left to be learned about these complex intracellular mechanisms (Rachal & Bohn, 2005).
A second mechanism believed to be responsible for opioid tolerance occurs via internalization of the opioid receptor from the cell membrane. The density of opioid receptors located on the cell membrane is governed by endocytosis, whereby the cell membrane closes around the receptor, effectively creating a bubble of cell membrane around the receptor and drawing it into the body of the cell. Once inside the intracellular environment the receptor can no longer function and is effectively down-regulated. Rats lacking one of these down-regulators (β-arrestin2) continue to have prolonged morphine-induced analgesia, whereas their counterparts that do have this down-regulator develop “tolerance” to the analgesic effects (Bohn et al., 2002; Bohn et al., 1999). Despite this evidence, some researchers have suggested that increased internalization may actually decrease tolerance by getting desensitized receptors off the membrane and causing desensitization through new or recycled receptors being substituted (Finn & Whistler, 2001).

Various opioid agonists (e.g., morphine, methadone, fentanyl) have been shown to differ in their ability to desensitize or down-regulate opioid receptors (Arden et al., 1995; Sim-Selley et al., 2000; Yabaluri & Medzihradsky, 1997). Some of these differences have been attributed to the “intrinsic efficacy” of the opioid agonist. Each opioid has a given level of intrinsic efficacy for the various opioid receptors. Intrinsic efficacy is a conceptual parameter that relates the number of receptors occupied to the magnitude of the receptor-mediated response. To generate a given effect, it is necessary to occupy a number of receptors out of the total population, the so called “fractional receptor occupancy” (Chavkin & Goldstein, 1982; Mercadante, 1999). The number of receptors that need to be occupied to create an analgesic effect is believed to be inversely proportional to the intrinsic activity; in other words, the larger the number of unoccupied receptors (receptor reserve) that exist when a drug achieves analgesia, the greater the intrinsic efficacy of the drug (Chavkin & Goldstein, 1984; Duttaroy & Yoburn, 1995; Ivarsson & Neil, 1989; Sosnowski & Yaksh, 1990).

In general, continuous treatment with opioids with lower intrinsic efficacy, such as morphine, have been known to cause a larger rightward shift in dose response (i.e., tolerance) (Saeki & Yaksh, 1993). Animal studies have shown that chronic treatment with high-efficacy opioids that have a significant receptor reserve, such as fentanyl, down-regulate fewer receptors (Sosnowski & Yaksh, 1990). However, recent studies show high-efficacy opioids actually activate more receptor-desensitizing substances (G protein-coupled receptor kinases) than low-efficacy opioids (Terman et al., 2004), leaving us again with more complexity than clarity on these opioid-related intracellular mechanisms.

**OPIOID-INDUCED HYPERALGESIA**

Opioid-induced hyperalgesia is a condition manifested clinically as hyperesthesia (i.e., dramatically increased sensitivity to painful stimuli) and/or allodynia (i.e., pain elicited by a normally nonpainful stimulus). It occurs in some patients (and, in laboratory studies, animals) receiving chronic opioid therapy; the abnormal pain often arises from an anatomically distinct region and is of a different quality than the original pain problem (Ossipov et al., 2005). Clinical reports dating back to the late 19th century documented that hyperalgesia was associated with opioid dependence. Later clinical observations and studies suggested that pain sensitivity differs between persons with opioid addiction and those who are not addicted (Compton, 1994; Doverty et al., 2001). In the 1940s, hyperalgesia also was described as part of the opioid withdrawal syndrome. In the past decade, research indicated that hyperalgesia also occurred in the context of short-term and continuous therapy in which physical dependence and withdrawal did not play a role (Angst & Clark, 2006).

Several mechanisms associated with opioid-induced hyperalgesia have been identified. Glutamate-associated activation of N-methyl-D-aspartate (NMDA) receptors causes spinal neuron sensitization; this pronociceptive mechanism has been implicated in the development of neuropathic pain and opioid-induced hyperalgesia. The ability of NMDA receptor antagonists such as MK801 to block opioid-associated hyperalgesia provides further evidence that NMDA receptors are involved in hyperalgesic states (King et al., 2005; Mao, 2006; Ossipov et al., 2005).

Other studies have documented that hyperalgesia results from increased excitatory peptide neurotransmitters, such as cholecystokinin (CCK), which are released from neurons in the RVM and activate spinal pathways that up-regulate spinal dynorphin. Both of these substances act as pronociceptive agents (Dourish et al., 1988; Gardell et al., 2002; Vanderah et al., 2000; Vanderah et al., 2001; Xu et al., 1992). These and other excitatory neurotransmitters are believed to cause “central sensitization” that result in hypersensitivity of the spinal cord to nociceptive inputs from the periphery. In other words, pain signals being transmitted into the spinal cord become amplified as a result of the action of these neurotransmitters.
OPIOID-INDUCED TOLERANCE AND HYPERALGESIA: TWO SIDES OF THE SAME COIN?

The major clinical manifestation of opioid-induced tolerance and that of hyperalgesia are the same; that is, increasing opioid doses are necessary to achieve adequate analgesia (Angst & Clark, 2006; King et al., 2005; Mao, 2006). Moreover, there are similarities in the mechanisms that cause tolerance and hyperalgesia. For example, CCK-mediated changes in the descending modulatory pathways appear to contribute to both opioid-induced tolerance and hyperalgesia (King et al., 2005). There also is evidence that tolerance and hyperalgesia share common cellular mechanisms that are related to changes in NMDA receptors (Mao et al., 1994; Mao et al., 2002).

The similarities between mechanisms causing tolerance and hyperalgesia suggest that some targeted therapies can prevent or reverse both phenomena. While this strategy has been shown to be effective in preclinical and clinical studies, Mao urged caution with this approach (Mao, 2002; Mao, 2006). He pointed out that hyperalgesia is characterized by different clinical features than tolerance. These features include pain intensity that is higher than the severity of the original pain problem, pain that is poorly defined in terms of quality and location, and changes in pain threshold and tolerability. These distinct features indicate that at least some of the cellular mechanisms underlying tolerance and hyperalgesia differ between the two entities. Hyperalgesia represents increased sensitivity to pain, whereas tolerance may reflect decreased sensitivity to opioids. Most importantly, unlike tolerance, opioid-induced hyperalgesia would worsen after an increase in opioid dose, whereas pain related to tolerance would be relieved by an increase in opioid dose (Mao, 2002; Mao, 2006).

CLINICAL IMPLICATIONS

Pain management specialists are frequently called to consult on cases involving opioid tolerance or toxicities. Strategies for clinical management must be based on the current understanding of the complex mechanisms underlying these problems. Some strategies, such as the use of opioid-sparing therapies and opioid rotation, are currently used to prevent and treat tolerance and hyperalgesia, although the evidence supporting these practices is lacking. Other strategies such as the use of concomitant low-dose opioid antagonists to suppress G protein switching, inhibition of β-arrestin2 to prevent down-regulation, or the use of CCK and NMDA receptor antagonists to suppress pain facilitation pathways are still in preclinical or early clinical studies. Pain management nurses should understand the scientific basis for current and emerging therapies.

One of the most commonly used strategies to prevent opioid tolerance and hyperalgesia is the use of adjuvant drug therapies such as anticonvulsants and antidepressants, as well as nondrug therapies such as heat, cold, and exercise programs. This approach is the cornerstone of the “opioid-sparing” principle, which aims to minimize opioid doses while providing optimal pain relief. Although there is no hard evidence that receptor desensitization or down-regulation occurs with more intensity at higher doses of opioids, many pain specialists accept the premise that an opioid-sparing treatment plan is the first step in proactively minimizing side effects and opioid tolerance (Ho et al., 2006; Lauretta et al., 1999; White, 2005), despite evidence that challenges this principle (Kloke et al., 2000).

Opioid rotation is widely used as a treatment option to take advantage of “incomplete cross-tolerance” to recapture efficacy in a patient experiencing significant opioid tolerance or unusual sensitivity to opioid side effects. Several reports have documented success with this strategy (De Stoutz et al., 1995; Drake et al., 2004; Indelicato & Portenoy, 2002; Kloke et al., 2000; Thomsen et al., 1999), although the research evidence is weak, given the poor design and small samples that characterize studies evaluating this clinical maneuver (McNicol et al., 2003; Quigley, 2004).

Combining opioids with low-dose opioid antagonists to prevent hyperalgesia and tolerance is an active area of study that offers some promise that the cellular mechanisms of tolerance might be circumvented. Wang et al. (2005) and Terner et al. (2006) demonstrated a significant attenuation in opioid tolerance when low-dose naltrexone was added to a morphine regimen in rats. A recent randomized controlled trial (RCT) in 350 osteoarthritis patients showed a statistically significant advantage in pain relief over time for patients treated with the combination of oxycodone and naltrexone over oxycodone alone, a clinical outcome that has been suggested to result from the suppression of G protein switching (Chindalore et al., 2005; Crain & Shen, 2000; Wang et al., 2005). With further validation, this drug combination approach could be offered as a pre-emptive strategy in managing patients at risk of developing significant opioid tolerance.

The ability of CCK antagonists to prevent the development of hyperalgesia and tolerance has been suggested (King et al., 2005), largely based on studies with the CCK antagonist proglumide in animal models.
(Tang et al., 1984; Watkins et al., 1984). In several small clinical studies (Bernstein et al., 1998; McCleane, 2004; McCleane, 1998; McCleane, 2003; Price et al., 1985), proglumide appeared to enhance opioid analgesia; whether the augmentation was attributed to reversal of tolerance and/or amelioration of hyperalgesia is debatable. To date, there have been no RCTs that fully document the efficacy of proglumide as a promoter of opioid analgesia. Moreover, studies in patients with documented opioid tolerance or hyperalgesia would be needed to demonstrate the putative counteractive effects of CCK antagonists on opioid-induced tolerance and hyperalgesia. Thus additional research is needed before CCK antagonists can be recommended in clinical practice (McCleane, 2004).

Blockade of the NMDA receptor has been shown to reduce opioid-induced hyperalgesia and retard opioid tolerance development in both animal models and human case reports (Celerier et al., 2000; Clark & Kalan, 1995; Davis & Inturrisi, 1999; Eilers et al., 2001; Elliott et al., 1994; Gorman et al., 1997; Haley, Sullivan, & Dickenson, 1990; Mao et al., 1995; Mercadante, 1996). However, one recent RCT in chronic pain patients failed to demonstrate a reduction in hyperalgesia or tolerance after three months of concurrent treatment with morphine and dextromethorphan (an NMDA receptor antagonist) compared with with morphine alone (Galer et al., 2005). Methadone, a mu agonist which also is an NMDA receptor antagonist, has been examined as an agent that can potentially prevent tolerance and hyperalgesia (Morley, 1998). Several clinical reports indicate that rotation to methadone from other opioids enhances analgesia (Benitez del Rosario et al., 2004; Quigley, 2004; Viganò et al., 1996). In contrast, enhanced pain sensitivity in opioid addicts who are receiving methadone maintenance therapy is well documented (P. Compton et al., 2001; Doverty et al., 2001; Mao, 2006). Thus, the role for methadone in the setting of hyperalgesia awaits further research.

Ongoing investigations to further define the variants of genes encoding the mu opioid receptor and on the key proteins involved in receptor desensitization and down-regulation are intriguing. If there were a simple way to test for these genetic differences in patients in the future, clinicians might have a more rational approach to optimal drug selection and drug rotation in opioid therapy.

Clinical strategies to prevent or manage hyperalgesia start with early identification of the problem. Hyperalgesia should be suspected whenever repeated dose escalation fails to provide the expected analgesic effects or when there is an unexplained pain exacerbation after an upward titration of opioid. The index of suspicion is higher if the increased pain is consistent with hyperesthesia or allodynia and other obvious causes such as disease progression or acute insult are ruled out. Hyperalgesia should be treated by reducing dose or eliminating the offending opioid. Theoretically, a reduction in the opioid dose with or without adding a replacement opioid or a gradual rotation to an alternate opioid would result in a decrease in pain. As with opioid tolerance, no RCTs exist demonstrating the superiority of one opioid over another in avoiding hyperalgesia.

FUTURE DIRECTIONS AND SUMMARY

The molecular mechanisms underlying opioid tolerance and opioid-induced hyperalgesia are being investigated in research laboratories throughout the world. Based on the research accomplished to date, it appears that these two phenomena may be related but also have distinct features. Future scientific efforts will be directed at deepening our understanding of how adaptive responses by multiple neural systems work together to counteract the analgesic efficacy of commonly used opioids. Future pharmaceutical development will focus on blocking the facilitatory mechanisms that produce these adaptive changes in the endogenous nociceptive and antinociceptive systems in response to continual exposure to an opioid analgesic. Development of diagnostic tests for biomarkers or genotypes that will allow identification of the opioid best suited to an individual patient’s profile seems attainable within the not-too-distant future.

REFERENCES


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