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The Effects of Pain on Opioid Tolerance: How Do We Resolve the Controversy?

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How chronic pain affects the development of opioid tolerance has been a controversial issue from both clinical and scientific perspectives for the past 25 years. Some studies have shown that chronic pain inhibits the development of opioid tolerance (Colpaert, 1978; Colpaert et al., 1978, 1980; Portenoy and Foley, 1986; Portenoy et al., 1986; Sherman et al., 1981; Vaccarino et al., 1993), whereas others have concluded that pain does not affect or accentuates tolerance development (Connell et al., 1994; Gutstein et al., 1993, 1995; Houde et al., 1966; Kayan et al., 1969; Kayser and Guilbaud, 1985; Onofrio and Yaksh, 1990). This apparent contradiction has been difficult to reconcile. The two positions have very different implications, both mechanistically and in terms of clinical treatment. Dr. Colpaert, a long-time proponent of the idea that pain inhibits tolerance development, has proposed a new theory of opioid action in an effort to provide a theoretical framework for his data and to explain conflicting results.

His theory is based on the underlying assumption that tolerance to opioids does not exist. Instead, it is proposed that chronic opioid administration causes hyperalgesia. The opioid maintains its effectiveness, but the hyperalgesia creates the impression that the opioid has become less effective. Chronic pain is postulated to cause hypoalgesia, leading to the conclusion that opioids are more effective in chronic pain states. Another assumption of this model is the concept that the perception of pain is proportional to the difference between the signal caused by a noxious stimulus and the "baseline" signal intensity, which is the average signal received by the "system" in the pain-free state.

For a theory to serve as an accurate framework explaining physical phenomena, three conditions must be satisfied: (1) the underlying assumptions must be sound, (2) the hypotheses must adequately account for all available experimental data, and (3) alternate explanations must be considered and either refuted or effectively reconciled with the proposed theory. The preceding review (Colpaert, 1996) has an unique perspective on this subject and raises many interesting points worthy of further investigation and discussion. However, there are some issues concerning the underlying ideas, supporting evidence and alternative explanations for findings that deserve further consideration. It is hoped that this paper will help complete the presentation of several issues raised and provide counterpoints and different potential interpretations of the findings discussed in the preceding review.

First, the idea that neural coding for pain is the difference between activity evoked by noxious stimulation and nonnoxious baseline activity is not supported by experimental evidence. In fact, primary nociceptors are activated only once a certain threshold is reached. It is also believed that the supraspinal perception of painful stimulation requires activation of projection neurons above a threshold value (Woolf, 1994). Pain, the conscious appreciation of nociceptive stimulation, requires integration of signals at many levels of the neuraxis. The function of signaling elements at each of these levels must be carefully considered and integrated into any underlying theory. Based on the initial assumption, a series of equations were generated to describe various aspects of nociceptive and opioid-induced responding. "Scenarios" were produced using values provided by the author, which produced the desired results. At no point was it stated (*a*) how the equations or the values provided were derived or (*b*) whether these equations, once generated, could quantitatively account for previous experimental and clinical data. Another deficiency of this assumption is the failure to consider the phenomena of central and peripheral sensitization. These concepts imply that the "gain" of the "system" may change, in that a given acute noxious stimulus may generate different physiological responses under different circumstances. Moreover, accepting the author's pain coding model and following his line of reasoning leads to several incorrect conclusions.

The first postulate derived from this model is that chronic opioid administration shifts baseline responses to the left, increasing the distance between baseline and nociceptive responses, which is perceived as hyperalgesia. However, there is no evidence that opioids suppress nonnoxious baseline sensory perceptions. If this were the case, one would expect opioids to function as anesthetics, not hyperalgesic agents. Thus, the physiological meaning or significance of a left shift in the normal

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* Abbreviations: SIA, stress-induced analgesia; HPA, hypothalamic-pituitary-adrenal; NMDA, N-methyl-D-aspartate.

baseline is not clear. It is also not clear what effect opioids would have on nociresponsive neurons that are inactive at "baseline." The idea that chronic opioids directly cause hyperalgesia is not generally accepted, with many studies (including some cited by the author) (Gutstein et al., 1995; Kayser and Guilbaud, 1985) showing that chronic opioid administration itself does not cause hyperalgesia. It is also hard to understand how hyperalgesia could be a property of both opioid administration and withdrawal, which is generally thought to consist of effects opposite to (or those suppressed by) opioids. However, an intriguing variation of this hypothesis has been put forward by others suggesting that opioids could induce a state of *latent* sensitization/hyperalgesia (Basbaum, 1995; Mao et al., 1995b). In this model (also discussed later in this commentary), opioids are thought to exert their inhibitory effects throughout chronic exposure, and the diminution of opioid effect (such as the increase in cyclic adenosine monophosphate levels and the decrease in analgesic effect) is because of compensatory responses either in neurons or neuronal systems. Removal of opioids (or decrease in effect between intermittent doses) would then unmask a compensatory hyperresponsiveness, which could lead to hyperalgesia and other withdrawal symptoms.

The second postulate of system theory is that chronic pain shifts the baseline stimulus perception to the right, causing a hypoalgesic state. This is also a difficult assumption to accept for several reasons. First, there is ample evidence that chronic nociceptive input causes hyperalgesia (Kayser and Guilbaud, 1985; Wiertelak et al., 1994). The evidence cited in support of hypoalgesia mainly refers to the phenomenon of counterirritation. That work is not directly relevant to the author's postulate because the pain stimuli used were not chronic. In fact, the literature suggests that the perception of chronic pain is reduced by an acute noxious stimulus, not vice versa. An unusual conclusion that could also be drawn from the concept of a shift in "baseline" input with chronic pain is that all chronic pain should resolve spontaneously, because the shift of the "baseline" would correspond to the magnitude of the chronic pain.

This assumed hypoalgesic effect of chronic pain is also used to explain observed increases in opioid effectiveness in chronic pain states. Supporting evidence for this point (as well as for much of the theory) was derived from the inflammatory polyarthritis model induced by *Mycobacteria butyricum* injection in the tail base. This model produces a serum-sickness-like illness, with multiple metabolic and physiological derangements in addition to an inflammatory polyarthritis. Therefore, it is difficult to determine whether changes in nociceptive responding (and other systems, such as the respiratory data cited by the author) are caused by the underlying disease process or by the pain itself (Dubner, 1994). For these reasons, this model has been generally abandoned in favor of other paradigms. The issue the author raises about whether constant nociceptive input is truly present in animal models of chronic pain is important, but this also applies to the polyarthritis model used in his studies. Other chronic pain models, such as the neuroma and nerve ligature/injury paradigms (Bennett and Xie, 1988; Seltzer et al., 1990; Wall et al., 1979) were not adequately reviewed, and the actions of opioids in these paradigms were barely considered. Again, literature suggesting decreased opioid effectiveness (or ineffectiveness) with chronic pain is not adequately evaluated, and other explanations for conflicting results, such as peripheral analgesic effects of opioids (Kayser et al., 1995; Stein, 1993), stress-induced analgesia (Terman et al., 1984), decreased opioid effect caused by chronic nociceptive stimulation (Mao et al., 1995a), or the modulation of "anti-opioid" peptide systems that affect the degree of analgesia produced by opioids (Rothman, 1992) are not satisfactorily discussed.

Finally, another basic assumption made by the author, that pharmacological tolerance to opioids does not occur, is debatable. There are many data to suggest that tolerance to opioids does occur at the cellular level and in the behaving organism (Cox, 1991; Cox and Werling, 1991; Nestler, 1992). Although it is known that conditioning and environmental factors can influence tolerance development (Trujillo and Akil, 1991), a convincing demonstration of pure pharmacological tolerance has been made in spinalized animals (Gutstein and Trujillo, 1993). However, perhaps the most disturbing potential consequence of this theory is that in an effort to match analgesia to the painful stimulus to avoid "apparent" tolerance development, clinicians would end up undertreating chronic pain. In summary, although Dr. Colpaert's theory raises some thought-provoking ideas, system theory as currently presented seems incomplete: the underlying assumptions can lead to physiologically inaccurate conclusions, the hypotheses do not completely explain all experimental data, and alternative hypotheses are not completely explored and reconciled with the theory. However, the need to reconcile the opposing clinical and experimental conclusions regarding the effects of pain on opioid tolerance remains. Better understanding of the interactions between pain and opioid tolerance could have implications of great importance, both for understanding mechanisms of pain and opioid signaling and for the treatment of patients suffering from chronic pain. How might these conflicting conclusions be resolved?

One important factor to consider is the differences in the nociceptive paradigms used. Some studies cited used intermittent administration of noxious stimulation (Abbott et al., 1981; Colpaert, 1978; Colpaert et al., 1978, 1980; Sherman et al., 1981; Vaccarino et al., 1993), which may not be analogous to chronic pain states. Also, as alluded to in the theory, different types of noxious stimulation may be perceived via different neural mechanisms and therefore might have different sensitivities

to opioids. For example, a study by Abbott et al. (1981) did not demonstrate tolerance development in the formalin test at doses that caused tolerance in the tail flick test. In a later study, they demonstrated that lower doses of opioid induced tolerance in the formalin test (Abbott et al., 1982). In addition, different nociceptive stimuli may differently engage endogenous analgesia and/or anti-analgesia systems (Watkins and Mayer, 1982), also affecting the development of tolerance. Therefore, the nociceptive paradigms used and the opioid doses used must be carefully considered when evaluating studies of this type.

In addition to evaluating the dose of opioid used to induce tolerance, the route of opioid administration and the presence of situational cues that affect the development of associative tolerance must also be considered (Baker and Tiffany, 1985; Grisel et al., 1994). For example, the temporal relationship of drug administration to nociceptive stimulation could be important in resolving conflicting results. A study by Vaccarino et al. (1993) showed minimal tolerance development when morphine was administered in the presence of formalin pain. When morphine was given 6 h before formalin, tolerance developed rapidly. Colpaert et al. (1978, 1980) also demonstrated an inhibition of tolerance development when opioid administration was accompanied by noxious stimulation. In general, studies that pair a repeated acute, intense noxious stimulus with intermittent opioid administration show attenuation of tolerance development.

It is also likely that stress affects opioid tolerance development. The handling and pain associated with opioid administration could induce stress-induced analgesia (SIA)[a] (Akil et al., 1976; Madden et al., 1977). Severe psychological, physical, and nociceptive stressors have been shown to cause SIA (Terman et al., 1984; Watkins and Mayer, 1982). Interestingly, tolerance can develop to some types of SIA over time (Akil et al., 1976; Madden et al., 1977). Investigators have evaluated interactions between stress, opioid analgesia, and the development of opioid tolerance. These studies showed that psychological and nociceptive stressors accentuated opioid analgesic effects (Appelbaum and Holtzman, 1984) and inhibited tolerance development (Takahashi et al., 1988, 1989; Takahashi and Kaneto, 1991). Glucocorticoids have been shown to be necessary for analgesia enhancement and the development of tolerance. However, administration of exogenous steroids in the absence of a stressor does not inhibit tolerance development (MacLennan et al., 1982; Sutton et al., 1994; Takahashi et al., 1989). Another study by Vaccarino and Couret (1995) also compared the development of tolerance in the presence of formalin pain in rats with impaired and normal hypothalamic-pituitary-adrenal (HPA) responses to stress. Animals with normal HPA responses did not develop opioid tolerance, while the abnormal responders developed tolerance. This led the authors to conclude that HPA activation was necessary for tolerance inhibition. To further investigate this possibility, we performed a study using peripheral inflammation and opioid pelleting to avoid effects on pain responsiveness that could be induced by handling and repeated noxious stimulation. Also, animals only underwent analgesic testing once to minimize associative effects. Although these animals had elevated corticosterone levels, indicating HPA axis activation, tolerance development was not inhibited (Gutstein and Akil, in preparation). Thus, it appears that glucocorticoids are necessary but not sufficient for the inhibition of tolerance development and that activation of the HPA axis per se does not appear to play a significant role in this inhibition. Possibly, glucocorticoid-dependent activation of an endogenous analgesic system in response to certain environmental cues, or, conversely, inhibition of an anti-analgesic system (see next paragraph) could explain the tolerance inhibition seen in the Vaccarino (Vaccarino and Couret, 1995) study. Identifying the factors responsible for the modulation of such systems will be an important direction for future research.

In addition to endogenous analgesic systems discussed above, several "anti-analgesic" systems have been described, of which the cholecystokinin system is probably best characterized at present. These systems function to diminish the analgesic effects of opioids, but do not cause hyperalgesia in the absence of opioids (Reinscheid et al., 1995; Rothman, 1992; Wiertelak et al., 1992). Environmental cues have been shown to be important in the activation of these pathways. A set of elegant experiments demonstrated that administration of opioids in the presence of signals that indicate a "safe" environment diminished opioid analgesic effects by a cholecystokinin-mediated mechanism (Wiertelak et al., 1992). Perhaps administration of the opioid concurrently with the nociceptive stimulus could be perceived as "unsafe," inhibiting the anti-opioid system and thus inhibiting the development of tolerance. Interestingly, Kaneto's group has recently shown that diazepam and the γ-aminobutyric acid-A receptor agonist muscimol could reverse the inhibition of opioid tolerance seen in mice when morphine was given in the presence of formalin pain (Rahman et al., 1994, 1995). They proposed that "pain-associated anxiety" could be a factor inhibiting tolerance development. It will be important to further characterize these responses and to determine whether situation-specific engagement of endogenous analgesic systems or inhibition of anti-analgesic systems could help reconcile conflicting clinical and scientific observations. Better understanding of these interactions could lead to important therapeutic advances in chronic pain treatment.

Peripheral effects of opioids may also affect observed opioid efficacy and tolerance development. Opioid receptors have been demonstrated on peripheral nerves (Fields et al., 1980) and have been shown to be respon-

sive to peripherally applied opioids and locally released endogenous opioid compounds when "up-regulated" during inflammatory pain states (Stein et al., 1991, 1993). During inflammation, immune cells that release endogenous opioids are present near sensory nerves, and a perineural defect allows opioids access to the nerves (Stein, 1993, 1995). It also appears that this mechanism may be operative in neuropathic pain models (Kayser et al., 1995), perhaps because of the presence of immune cells near damaged nerves (Monaco et al., 1992) and possibly because of the presence of perineural defects in these conditions. It will be important to determine whether tolerance develops to peripheral opioid effects.

As previously mentioned, it has also been demonstrated that there may be interactions between the cellular mechanisms underlying hyperalgesia and the development of morphine tolerance. Research in this area was spurred by the findings that N-methyl-D-aspartate (NMDA) receptor antagonists could inhibit both (*a*) the development (but not the expression) of narcotic tolerance and dependence (Trujillo and Akil, 1991, 1994) and (*b*) the development and expression of thermal hyperalgesia in various pain models (Coderre et al., 1993; Mao et al., 1995b). If similar neuronal mechanisms were responsible for both phenomena, one would predict that the presence of hyperalgesia would decrease opioid effectiveness (in contrast with the concept presented in the previous paragraph). There are data to suggest that under some conditions, this decrease in efficacy can be observed (Gutstein et al., 1995; Mao et al., 1995a). Also, one could speculate that chronic opioid administration, via NMDA receptor activation, could cause a "compensatory" hyperalgesia resulting in diminished opioid effect over time and a hyperalgesic response when opioids were withdrawn. Under certain conditions, hyperalgesia has been demonstrated after chronic morphine administration (Mao et al., 1994; Ohnishi et al., 1990). These studies used intermittent administration paradigms and behavioral testing several half-lives after the last drug administration, suggesting that the observed hyperalgesia actually could be a withdrawal sign. This concept could have important implications for opioid treatment schedules in chronic pain patients. However, the general applicability of this model and some details of the proposed mechanism remain to be determined. Reasons for differences in the expression of morphine tolerance and hyperalgesia (for instance, why hyperalgesia, but not tolerance, is reversible after a single dose of NMDA receptor antagonist) and interactions of other messenger systems activated by opioids and pain must be further investigated. In addition, other causes of reduced opioid efficacy, such as anti-opioid peptide systems, may not share a common mechanism with this phenomenon. As always, efforts must be made to reconcile the implications of these findings with contradictory results generated using other paradigms.

In conclusion, there are many variables that may modulate both nociceptive responses and opioid signaling. Differences in type, intensity, and duration of noxious stimulation may cause different neurochemical changes in the organism and lead to different response states of both pain signaling and analgesia systems. Similarly, differences in dose, route of administration, and timing of opioid relative to pain may influence analgesic responses elicited by opioids and their long-term effectiveness in the treatment of chronic pain. However, while impressive progress has been made, distilling these divergent data and hypotheses into a unified theory of pain and opioid function still seems a daunting task. The system theory presented in the previous review (Colpaert, 1996), although not entirely comprehensive as currently formulated, raises interesting issues for discussion and investigation. Future studies should reveal novel underlying themes and mechanisms useful for integrating this mass of disparate observations into a more cohesive whole. This area of research provides an unique opportunity for integration of molecular, anatomic, and behavioral approaches. Understanding the neural substrates and molecular mechanisms underlying behavioral responses to pain and opioids should provide us with new therapeutic opportunities to more effectively relieve pain and suffering; this is the ultimate goal of every researcher and clinician involved in the interesting but often frustrating field of chronic pain.

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