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Pleasure into pain: The consequences of long-term opioid use

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Abstract

One consequence of repeated drug administration is the development of adaptations in the nervous system, sometimes termed 'drug-opposite' responses. During administration, the effects of the drug are diminished by these adaptations (tolerance), while cessation of drug use results in the emergence of these drug-opposite responses as the withdrawal syndrome. Recent evidence on pain responses challenges this simple notion of withdrawal and suggests that aversive drug-opposite states may play a more important role in drug dependence than previously thought. While opioids such as heroin produce analgesia, people with a history of opioid self-administration are hypersensitive to certain kinds of pain during the time they are under the influence of the analgesic drug. This suggests that in pain systems, the drug-opposite response exceeds the pain inhibiting effect of the drug itself. This hyperalgesia is evident in people with a history of heroin use and is not modified by methadone or buprenorphine treatment but is reduced by long-term abstinence from opioids. This same pattern of the drug-opposite response exceeding the drug effect may also occur for mood. While opioids cause elevation of mood, commonly described as euphoria and reduction of emotional distress, methadone maintenance participants show significant negative mood disturbance relative to controls. Thus, for pain and mood, the chronic opioid user under the influence of the drug does not experience an opioid effect diminished by tolerance but a state opposite to the effect of the drug. Increases in drug concentration arising from administration serve only to reduce the degree of pain and mood disturbance. These aversive pain and mood states may contribute to the motivation for continued drug use and the dysfunction associated with drug dependence.

Keywords: Opioid; Methadone; Mood; Pain

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Tolerance and physical dependence play important roles in our understanding of drug dependence. Both arise as a result of repeated administration of drugs such as opioids. Physical dependence only becomes evident on cessation of drug use when the person experiences a withdrawal syndrome, although evidence of acute physical dependence (e.g., Wright, Bigelow, Stitzer, & Liebson, 1991) suggests that this may not necessarily require prolonged drug exposure. The prevention and amelioration of withdrawal can be major motivating factors for continued drug use in dependent users. Tolerance is important for several reasons: Initial tolerance to adverse effects of drugs (e.g., the nausea caused by heroin administration or inhalation of tobacco smoke) may be necessary before the positive effects of the drug become prominent, while tolerance to the positive effects leads to escalation in the amount and frequency of drug use. Thus, tolerance and physical dependence play roles from the initial experimentation stage through well-developed dependence.

For some time, tolerance and physical dependence have been viewed as arising from adaptations in the nervous system that result from drug exposure. This was described in terms of 'drug-opposite' responses in the opponent process model (Solomon & Corbit, 1974). Kalant, LeBlanc, and Gibbins (1971) also hypothesized that the adaptations leading to tolerance were the basis for withdrawal reaction that occurred on cessation of drug administration. As noted by Kalant et al. (1971), one major piece of evidence that a common set of processes underlie tolerance and physical dependence is the fact that withdrawal signs and symptoms are almost always opposite to the direct effects of the drug. In the case of opioids, the direct effects of euphoria, analgesia, and constipation are replaced by dysphoria, hyperalgesia, and diarrhea.

The notion of an adaptation that is opposite to the drug response is illustrated in Fig. 1. For simplicity, this is represented as a single, prolonged episode of drug administration during which drug concentration is constant. In the absence of any adaptation, there is an increase in drug effect that commences at the time of drug administration. If we assume that a constant drug concentration is achieved and maintained over a period of time, then drug effect will also be constant. With the termination of drug administration, drug concentration falls and with it the drug effect in a proportional manner. In the bottom panel, tolerance and withdrawal are included in the model. Tolerance commences soon after drug administration and develops most rapidly in the first period of drug of administration before a much slower rate of decline (Ouellet & Pollack, 1997). On cessation of drug administration, a drug-opposite response replaces the drug effect before eventually diminishing in intensity. This pattern can be explained if there is an adaptive response to the drug that has the following characteristics: The response is opposite to the drug effect or homeostatic in nature (Poulos & Cappell, 1991), it develops very soon after drug administration and it diminishes in intensity after cessation of drug administration, but only with some lag time.

Early accounts of the adaptations underlying tolerance and physical dependence came at a time when the biological processes mediating the adaptations to drugs of abuse were not well understood. More recently, a number of these adaptational changes have been well described, particularly for opioid drugs. Adaptations occur at the intracellular level,

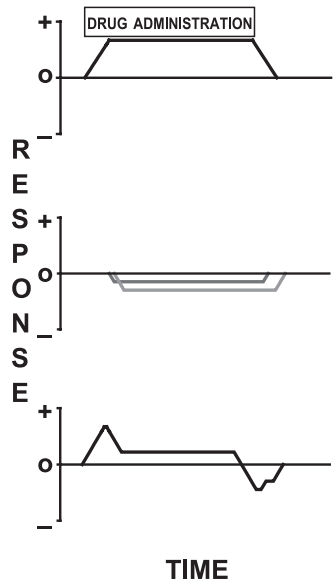

Fig. 1. The three panels illustrate a model of conventional adaptation to a drug in which a hypothetical drug is administered so as to achieve a constant concentration over a period of time. The upper panel shows the increase in effect with initial administration, a plateau when steady-state concentration is achieved, and then a decline when drug administration ceases. Potential drug-opposite or adaptational responses are represented in the middle panel. The sum of the concentration-related drug effect in the upper panel and the adaptational responses in the middle panel is shown at the bottom. Drug effect increases with concentration but then declines due to adaptation (tolerance). With cessation of administration, there is a lag time before adaptational responses cease, resulting in a drug-opposite or withdrawal state.

at the systems or multicellular level, and may also be conditioned (Koob & Bloom, 1988; Nestler & Aghajanian, 1997). Of these, the intracellular adaptations leading to opioid tolerance and physical dependence have been best described. Opioids act via the G-protein coupled μ-opioid receptor to inhibit the action of adenylyl cyclase, reducing the activity of cAMP and protein kinase A. The main consequence is a general inhibition of neuronal activity. Adaptations have been demonstrated at almost all points in this cascade: decreased numbers of μ-opioid receptors, uncoupling of the μ-opioid receptor and the G-protein, increased concentration of adenylyl cyclase, and increased protein kinase activity (Williams, Christies, & Manzoni, 2001). Other adaptations, including cellular remodeling (Robinson & Kolb, 1999; Robinson, Gorny, Savage, & Kolb, 2002), may also develop over time. Thus, a more contemporary model of tolerance and withdrawal should include multiple adaptations, each with different time courses of onset and offset (some may begin within minutes of drug administration, others may develop only over days or longer). This is represented in Fig. 1 by the two types of drug-opposite response. One shows characteristics of more rapid onset after drug administration and more rapid offset after cessation of administration, while the other exhibits greater delays in onset and offset.

1. Tolerance to opioid effects in methadone maintenance patients

People who are heroin dependent show marked tolerance to the effects of all opioid drugs. This is evident from the doses of heroin they typically administer; these doses would produce respiratory depression, vomiting, sedation, and possibly coma in a nontolerant person. When such people elect to participate in methadone maintenance programs, their tolerance and physical dependence are maintained but with a controlled, regular dosing regimen. Tolerance can be inferred where the effects of methadone in the maintenance population are relatively small compared to what a similar dose of methadone would produce in an opioid naïve person. Changes in opioid effect can also be observed with fluctuations in methadone concentration.

We have carried out a number of studies in methadone patients in which a range of responses are measured at multiple time periods over a single dosing interval (24 h) and blood samples are collected for the determination of plasma methadone concentration. The degree of fluctuation in methadone concentration varies from individual to individual, but the typical pattern is to show a rise in concentration following oral administration of the drug, with a peak reached approximately 3 h after administration. The concentration then drops, initially at a higher rate and then at a slower rate over the remaining period of the dosing interval. The greatest concentration differences, and therefore the greatest differences in response, occur between the period immediately prior to dosing (at the time of trough methadone concentration) and around 3 h later (at time of peak methadone concentration). The results of these studies have shown that despite the aim of methadone maintaining a constant effect throughout the day, there is significant fluctuation in a range of responses from trough to peak. These include physiological responses (e.g., respiration rate, pupil size) and subjective changes (e.g., withdrawal symptoms, mood) (Dyer et al., 1999).

Based on our conventional understanding of opioid tolerance, we would expect the various measures to show that methadone maintenance patients would still experience an opioid effect at time of trough methadone concentration. That is, methadone maintenance patients will differ from nondependent people not administered an opioid drug. As a result of chronic opioid exposure and consequent tolerance development, this opioid effect may be of relatively small magnitude. Furthermore, this opioid effect should increase from time of trough concentration to time of peak concentration, reflecting the increased concentration of methadone. Our results have shown evidence of this pattern for a number of measures (Dyer et al., 1999; Newcombe, Bochner, White, & Somogyi, in press). For example, opioids have a prominent respiratory depressant effect and the respiration rates of patients maintained on methadone are below those of controls. Increases in methadone concentration from trough to peak further decrease respiratory rate in the methadone group.

It is important to note the profound tolerance shown by these patients: Even the lowest concentrations of methadone in a 24-h period would be fatal to a nondependent subject as a result of respiratory depression. What is evident from these data is that there is pronounced tolerance to the effects of opioids on respiratory rate in methadone maintained patients based on the small differences between controls and methadone patients at time of trough concentration. It is also clear that methadone patients are still responsive to changes in

concentration that occur from time of trough to time of peak concentration, even though this change occurs on a daily basis. A similar pattern is evident in other measures; for example, the reduction in pupil diameter produced by opioids such as heroin and methadone is still present in methadone patients and there is a further reduction from time of trough to time of peak concentration.

2. Pain responses in methadone maintenance patients

One of the original measures used to evaluate opioid effects over the 24-h methadone dosing interval was response to pain produced by electrical stimulation. This produced results very similar to those described above for respiration; that is, methadone patients exhibited pronounced tolerance, but there was a residual analgesic effect of methadone at time of trough concentration with an increase in the effect at time of peak concentration (Dyer et al., 1999). Like the other measures, electrical stimulation analgesia is an opioid effect that conforms to our conventional understanding of tolerance. In contrast, more recent data collected on cold-pressor pain show a very different pattern to that for electrical stimulation and for the other measures of opioid effect. Cold-pressor pain behaves in a manner different from our conventional understanding of tolerance and may be a model for a subset of responses that appear to behave in this atypical manner.

Opioids such as heroin and methadone act to decrease pain. Based on our conventional understanding of tolerance, methadone patients would be expected to be less responsive to pain than controls. At the time of trough concentration, the difference between methadone patients and controls may only be small as a result of their chronic opioid exposure and consequent tolerance, but the difference would be larger at time of peak concentration. Instead, the results show a very different pattern. In particular, at time of trough concentration, methadone maintenance patients are hypersensitive to cold-pressor pain. Using our cold-pressor model, the maximum time that control subjects were able to keep their arm immersed in the ice-cold water was 56 s, but for methadone patients the mean value at time of trough concentration was 15 s (Doverty, White, et al., 2001). This is a difference of over threefold in the direction opposite to that expected based on a conventional model of tolerance. Indeed, it could be said that for cold-pressor pain, methadone patients are constantly in a state of withdrawal (i.e., experiencing the ‘drug-opposite’ response of hyperalgesia) rather than experiencing an analgesic response reduced in intensity because of tolerance.

While somewhat surprising, this finding is consistent with other published results. As early as 1965, Martin & Inglis described significantly lower duration for the cold-pressor test in an incarcerated sample of female ‘‘known narcotic addicts’’ as compared to matched ‘‘non-addict’’ controls. Ho and Dole (1979) found that drug-free ex-addicts and methadone-maintained patients were more pain sensitive (as their pain threshold values determined in a cold-pressor test were significantly lower) than drug-free controls. Pain-sensitive subjects (as defined by their response to the cold-pressor test) were found to be overrepresented among current and past drug abusers, including those in methadone treatment programs for opioid

dependence (Compton, 1994). In contrast, results from some other types of pain induction show results similar to electrical stimulation. Using pain induced by mechanical pressure, Schall, Katta, Pries, Kloppel, and Gastpar (1996) found that at time of trough concentration, methadone patients showed pain sensitivity very similar to the control values. As methadone concentration increased, there was evidence of analgesia, with significantly decreased pain response at time of peak methadone concentration compared to controls.

While hyperalgesia is opposite to what may be expected, methadone patients still respond to changes in methadone concentration and to the administration of a different opioid. For methadone maintenance patients receiving their daily dose, the increase in methadone concentration results in an increase in maximum duration in the cold-pressor test—the expected analgesic effect. While statistically significant, the increase is relatively small in magnitude (Doverty, White, et al., 2001). As a result, the duration of immersion for methadone patients at time of peak concentration is less than half the value for nondependent subjects who have not been administered an opioid drug. Thus, the hyperalgesic methadone patients could be considered in a 'withdrawal state,' whether at time of trough or peak concentration, but the withdrawal is less intense at the time of peak concentration. There is also a response to administration of a different opioid when morphine is administered at a level greater than that used clinically for analgesia: It produces a small analgesic effect, but again the values for cold-pressor duration are significantly below those of control subjects (Doverty, Somogyi, et al., 2001). In summary, methadone patients are profoundly hyperalgesic to cold-pressor pain, indicative of a 'withdrawal' state during drug administration, and show marked tolerance to the analgesic effect of opioid administration.

3. Hyperalgesia in methadone maintenance patients: cause and consequence

The evidence from our group and others that methadone patients are hyperalgesic to cold-pressor pain when compared to controls raises the issue of the generality of this phenomenon. Subsequent to the study reported above, we have observed hyperalgesia in patients maintained on buprenorphine (Compton, Charuvastra, & Ling, 2001) and slow-release oral morphine (Bochner, Mitchell, White, & Somogyi, 2003) and in heroin-dependent patients entering treatment (Ling et al., 2003). Hyperalgesia is therefore not a product of methadone maintenance but seems to be associated with long-term use of a range of opioids. It would appear from our observations that heroin-dependent patients enter treatment with established hyperalgesia and that subsequent maintenance on methadone or buprenorphine does not reverse that hyperalgesia, but also does not make it worse.

These results imply that hyperalgesia can be induced by long-term opioid administration, but they do not exclude the possibility that hyperalgesia is a predisposing factor leading to opioid dependence or that there is a genetic or other predisposing factor that leads to both hyperalgesia and opioid dependence. These hypotheses could, in theory, be tested directly by chronic administration of opioids to a group of healthy control study participants, but it is clearly unethical to do so. Therefore, we need to rely on indirect evidence. There are several lines of evidence suggesting that hyperalgesia is caused by prolonged opioid administration.

Firstly, Compton (1994) found that abstinent drug abusers were able to tolerate cold-pressor pain more than currently using subjects. In this study, cocaine users were included together with opioid users so the data can be regarded as suggestive only. However, more recent evidence confirms that ex-opioid users (at least 6 months abstinent) have decreased pain sensitivity compared to controls (Hay et al., 2003). If, as these results suggest, the hyperalgesia of opioid users is a reversible phenomenon, then it is unlikely that hyperalgesia is a stable, long-term trait caused by genetic or other factors.

The second line of evidence comes from pain patients treated chronically with opioids for analgesia. Our assessment of these patients (Hay et al., 2003) shows that the magnitude of cold-pressor hyperalgesia is approximately equivalent in pain patients administered opioids chronically compared to patients maintained on methadone for treatment of opioid dependence. It should be noted that some pain patients are hyperalgesic for reasons related to their particular medical condition, although hyperalgesia is not common to all people with chronic pain. However, the generality of hyperalgesia in unselected pain patients suggests that it may be a consequence of long-term exposure to opioids.

The third line of evidence comes from animal studies. There is increasing evidence from studies in several species of hyperalgesia arising from opioid administration. In many experiments, hyperalgesia is measured only after cessation of opioid use or administration of an opioid antagonist. This is equivalent to opioid withdrawal-induced hyperalgesia. However, Vanderah et al. (2001) demonstrated hyperalgesia during the time course of prolonged opioid administration. That is, in common with methadone patients, the animals showed evidence of hyperalgesia while the opioid (morphine) continued to be administered and hence significant concentrations of the analgesic drug were present. In this study, rats were implanted with subcutaneous morphine pellets, and hence there was no opportunity for drug-related conditioned responses. The animals' initial response to radiant heat showed analgesia (relative to animals implanted with placebo pellets), but by Day 4 there was clear hyperalgesia that was maintained for the remaining 3 days of implantation. When administered additional morphine, the animals showed an increase in latency indicative of analgesia. Thus, this study shows that prolonged opioid administration to animals is sufficient to produce pain responses similar to those of the methadone patients.

In summary, hyperalgesia occurs in populations chronically exposed to opioids, appears to be reversible on cessation of administration, and in an animal model can be demonstrated as a consequence of opioid administration. This evidence suggests that the hyperalgesia evidenced by methadone patients is opioid induced.

4. Mechanisms of opioid-induced hyperalgesia

In contrast to the model of tolerance and withdrawal presented in Fig. 1, pain responsiveness (as measured by the cold-pressor test in humans) is better represented by the model in Fig. 2. Here the adaptational response is of greater magnitude than the direct response to the drug so that there is a net decrease in response below baseline or control level. The term

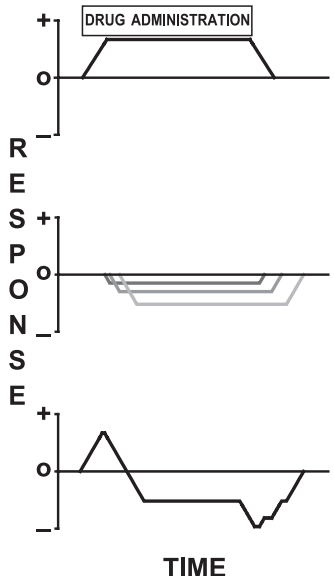

Fig. 2. The three panels illustrate a model of hyperadaptation in response to drug administration. The model is the same as in Fig. 1, except that the magnitude of adaptation (drug-opposite) response is greater, here illustrated as an additional response. As a consequence, initial drug administration produces a drug effect before the adaptational responses produce a drug-opposite state during the period of drug administration. The magnitude of this drug-opposite state increases when drug administration ceases (withdrawal) before a return to baseline.

hyperadaptation may best describe adaptational responses that exceed the original drug response in magnitude.

The difference from baseline increases further after drug administration ceases—the withdrawal phase—before eventually returning to normal. The relation between the duration of administration and the duration of withdrawal is unknown. For diagrammatic purposes, withdrawal is represented as an episode of relatively short duration, whereas in practice it is likely to be much longer.

A number of the potential mechanisms that may mediate ‘conventional’ adaptation leading to tolerance and physical dependence were described above. While these may still be important for hyperadaptation, it may be that additional mechanisms also play a role, leading to the exaggerated response. These additional mechanisms can be investigated using pain as a model system for hyperadaptation.

Understanding hyperalgesia relies on detailed knowledge of the various modulatory influences on activity in the ascending pain pathway. Afferent nociceptive fibers carrying pain impulses from the periphery terminate in the dorsal horn of the spinal cord. Axons of most of the dorsal horn neurons cross the cord and enter the lateral spinothalamic tract that joins the medial lemniscus in the medulla and projects to the thalamus from where the impulses are relayed to the somatosensory cortex. The descending pain-modulating pathway inhibits and facilitates the transmission of pain-related activity through its influence on the ascending pain pathway. It originates in the medulla and projects to the dorsal horn of the

spinal cord. The rostral ventromedial medulla contains populations of cells that inhibit pain perception (OFF cells) and those that facilitate pain perception (ON cells). This pain-modulating system is rich in inhibitory μ-opioid receptors activated by endogenous opioids and excitatory *N*-methyl-D-aspartate (NMDA) receptors activated by glutamate. Noradrenaline, serotonin, dopamine, and substance P (acting at NK-1 receptors) also play important modulatory roles in this pathway.

Hyperalgesia has been associated with dysfunction of the inhibitory pain regulation pathway and up-regulation of the pain-facilitating pathway, resulting in hyperexcitability of the dorsal horn neurons and enhanced pain perception (Porreca, Ossipov, & Gebhart, 2002). Vanderah et al. (2001) have provided convincing evidence that the mechanisms of opioid-induced hyperalgesia observed during chronic opioid administration involve the descending pain facilitation system (ON cells). They found that opioid-induced hyperalgesia could be blocked by microinjection of lidocaine into the rostral ventromedial medulla (to inhibit all neuronal activity in this area). Furthermore, bilateral lesions of the dorsal lateral funiculus (through which the descending facilitation projects to the dorsal horn neurons of the spinal cord) also blocked the opioid-induced pain. The central role of the μ-opioid receptor was shown by Li, Angst, and Clark (2001), who demonstrated that μ-opioid-deficient mice did not develop opioid-induced hyperalgesia while the control mouse strain developed opioid hyperalgesia under the same experimental conditions, and by Mao, Sung, Ji, and Lim (2002), who showed that the opioid antagonist naloxone blocked morphine-induced hyperalgesia.

These data suggest that opioid-induced hyperalgesia is a consequence of inappropriate tonic neuronal discharge in the ON cells originating in μ-opioid receptor-rich areas of the medulla, producing inappropriate descending facilitation of pain perception. This research highlights a particular neuronal pathway that, at least in an animal model, appears to be responsible for the hyperadaptation leading to hyperalgesia.

5. Mood states and withdrawal in methadone maintenance patients

In the case of pain, we have good evidence that the model of hyperadaptation fits the data and we also have potential mechanisms underlying the exaggerated drug-opposite response. If respiration, pupillary response, and electrical stimulation pain exhibit conventional tolerance, the question of the uniqueness or generality of the cold-pressor response arises. Does the hyperadaptation model apply to other drug effects or is it unique to certain kinds of pain response only and therefore of little interest in understanding the phenomena of drug dependence? While the evidence is not as extensive as it is for pain, there is some support for the notion that mood responds in the same way as cold-pressor pain, as do symptoms of withdrawal.

Changes in mood and subjective experience are understood to be one of the major reasons for use of opioid drugs (Jasinski, 1991). The most important changes in subjective experience produced by opioids are euphoria and diminished emotional distress. That is, there is both induction of a positive mood state and reduced negative mood states. Heroin users self-report that these changes are important reasons for continued use of the drug.

Based on a conventional model of tolerance and physical dependence, it would be expected that methadone maintenance patients would have somewhat elevated mood and/or less distress than controls and that increases in methadone concentration would be associated with an elevation of mood or decrease in mood disturbance. We have measured mood in patients maintained on methadone (Dyer et al., 2001) and on other maintenance opioid pharmacotherapies, including LAAM and slow release oral morphine. The results from methadone are typical of those from the other maintenance medications. These studies have utilized the Profile of Mood States (POMS). Subjects rate each item from a list of 65 adjectives according to how they are feeling at the time. There are six empirically derived subscales, five reflecting negative mood states (depression, tension, anger, fatigue, and confusion) and one reflecting positive mood state (vigor). A total mood disturbance score can be derived by summing these scores across the five negative mood states and subtracting the vigor score. An early study (Price, Moran, Crunican, Rothenberg, & Cutter, 1975) had shown that opioid users experiencing withdrawal at entry to treatment had considerable mood disturbance as measured by the POMS score. However, within 45 min of receiving methadone, the POMS scale showed changes indicative of a decrease in mood disturbance. Thus, the POMS scale is sensitive to changes in mood characteristic of opioid administration.

Subjects in our study were stable on methadone maintenance and were each tested over a single 24-h dosing interval. The POMS score was measured on 11 occasions over this time. Control subjects were not drug dependent and had data recorded over a 24-h period. Subjects on methadone maintenance showed higher scores (indicative of greater mood disturbance) for all of the negative moods and a lower score on the single positive mood (vigor). The total mood disturbance score showed a change from time of trough to time of peak concentration, with greater mood disturbance when methadone concentration was low and less mood disturbance (i.e., mood closer to controls) at time of high methadone concentration. Thus, despite the fact that opioid administration is associated with euphoria and diminished emotional distress, patients maintained on methadone show significantly more negative mood states than controls. However, increases in methadone concentration change mood in the direction of the controls, but the level of mood disturbance is still greater than for controls. Mood state thus resembles cold-pressor pain: It is characterized by a drug-opposite response (enhanced mood disturbance) during the period of opioid administration that may be due to the phenomenon of hyperadaptation but also responds in the expected manner to increases in methadone concentration.

Comorbid mood and anxiety disorders are common in opioid-dependent populations, and this could account for at least some of the difference from controls. However, there is earlier more direct evidence to suggest that chronic opioid administration may be associated with negative mood states. Martin et al. (1973) administered methadone to six subjects over 15 weeks. While the initial effects of methadone included euphoria, consistent with Price et al. (1975), longer term administration was associated with greater dysphoria. Similar effects have been found with repeated administration of heroin (McNamee, Mirin, Kuehnle, & Meyer, 1976; Mirin, Meyer, & McNamee, 1976; Mirin, Meyer, McNamee, & McDougle, 1976). While these studies are somewhat confounded by increases in dose of the opioid

administered over the period in which the response changes from euphoria to dysphoria, they are consistent with a change toward negative mood states with chronic opioid administration.

Another measure that shows evidence of a drug-opposite response during the time course of drug administration is the set of responses commonly used to measure withdrawal itself. While withdrawal is multifaceted and characterized by a range of physiological and subjective changes, it is typically measured with a limited range of signs and symptoms. We have developed and utilized a withdrawal scale that allows determination of changes within the time course of a single 24-h dosing interval (Dyer & White, 1997). This 16-item withdrawal scale has been used in studies with methadone patients similar to those described for mood (Dyer et al., 1999). The symptoms include yawning, stomach cramps, tense muscles, salivation, and craving. The results again show a counter-intuitive outcome. At time of trough methadone concentration, patients administered methadone have significantly higher withdrawal scores than controls. Not only do we expect no withdrawal during the time course of administration of an opioid, but the opioid should of course suppress any withdrawal symptoms. These results show evidence of withdrawal concurrent with evidence of opioid effect (e.g., diminished pupil diameter compared to controls). The increase in methadone concentration from trough to peak produces a change in the direction expected: a diminution in withdrawal severity so that the withdrawal scores of methadone patients approach those of controls.

For both mood and withdrawal score, there is evidence of hyperadaptation consistent with the results from cold-pressor pain. However, for these latter two measures, we have less supportive evidence and no clear neuropharmacological mechanism. Nevertheless, the data are convincing in showing that during methadone administration patients experience drug-opposite responses as negative mood states and withdrawal symptoms.

6. Implications for theory and practice

These findings have very important implications for understanding both the nature of dependence and the functional state of opioid-dependent people on admission to and during treatment. The suggestion that adaptation may be exaggerated for some responses leading to a drug-opposite or withdrawal-like state during drug administration is similar, in some respects, to the notion of hedonic homeostatic dysregulation. Koob and Le Moal (1997) characterized addiction in terms of a cycle of spiraling distress. One of the major drivers of this cycle is the adaptive change that occurs in response to drug administration. They also indicated that this could result in a change in hedonic 'set point,' with baseline affect reset to some lower level, although they did not predict dysphoria during drug administration. The results described here suggest that the magnitude of adaptive change is greater than that suggested by Koob and Le Moal (1997) and that our account of such changes should extend beyond hedonic state to other drug-related changes. In addition, the example of cold-pressor pain shows that we can measure the extent of adaptation, determine its reversibility, and isolate the neuronal substrate mediating the adaptational change. Further research on these neuronal substrates should help in understanding why the reaction to some drug effects is conventional adaptation

leading to tolerance during administration and withdrawal on cessation, while for others it is hyperadaptation, leading to a withdrawal-like state during drug administration.

It is clear from the results here that people dependent on opioids cannot be characterized as simply experiencing diminished opioid effects due to tolerance. Rather, they are best characterized as being, at least for some measures, in a constant state of withdrawal that is diminished partly by further opioid administration. This suggests that patients would be expected to be extremely dysfunctional simply based on the fact that they experience these drug-opposite responses on a constant basis. A state of pronounced negative mood, hypersensitivity to pain, and the physiological and subjective disturbance characteristic of withdrawal is likely to make normal social functioning extremely difficult. This level of dysfunction will be coupled with fluctuations in the severity of disturbance according to the level of opioid present. When heroin is being used the rate of fluctuation will be rapid, while methadone and buprenorphine will markedly reduce the rate of change.

This account suggests that stabilizing patients on a maintenance agent such as methadone or buprenorphine achieves only part of the process of reversing addiction. The hyperadaptational state will still be present, negatively influencing the person's ability to function normally. We still lack an effective approach to reducing this hyperadaptation through pharmacological or other means. Until this can be achieved, our focus should be to maximize the ability of opioid-dependent people to cope with the level of disturbance they experience.

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