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A Two-Separate-Motivational-Systems Hypothesis of Opioid Addiction

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BECHARA, A., K. NADER AND D. VAN DER KOOY. *A two-separate-motivational-systems hypothesis of opioid addiction.* PHARMACOL BIOCHEM BEHAV **59**(1) 1–17, 1998.—There has been a long debate as to whether opioids are sought for withdrawal relief or for their ability to serve as incentives in their own right. We suggest that independent motivational systems mediate the rewarding effects of opioids in the nondependent state and in the physically dependent/withdrawal state. In the opioid-dependent state and the presence of opioid withdrawal, the rewarding effects of withdrawal relief inhibit or mask the acute rewarding effects initially exerted in the nondependent state, but the acute rewarding effects are unmasked after the alleviation of withdrawal. © 1998 Elsevier Science Inc.

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VARIOUS models have been applied to the phenomenon of compulsive drug use but most emphasize one of two possibilities. The first attributes drug motivation, especially with drugs that produce physical dependence such as opioids, to the need to alleviate the withdrawal distress resultant from a history of drug use (54). The other incentive possibility stresses druglike rather than drug withdrawal states as the most powerful instigator of drug use, and drug motivation occurs in the absence of withdrawal and independent of any drug history (116,135).

The view that withdrawal and physical dependence are the prime instigators of opioid intake was challenged by an incentive motivational view (116,135) for several reasons. First, the withdrawal view did not explain why drug self-administration habits get established in initially nondependent humans (138) and animals (15,116). Second, the relief of withdrawal distress is only minimally effective in treating addictive syndromes in clinical settings (19,39,122,132), although it may be difficult to relieve withdrawal completely. Third, proponents of the incentive view argue that the self-administration of drugs generally occurs when the drug stimulus is still present in the brain rather than when the last drug injection is fully metabolized and the withdrawal condition is fully established (116).

Although the evidence that withdrawal and physical dependence are not necessary conditions for opioids to be sought and self-administered is substantial (116,135), the possibility that withdrawal may be a sufficient condition for the maintenance of opioid administration in physically dependent subjects has never been ruled out. Indeed, there is a strong evidence in support of the view that once an opioid addict becomes physically dependent, tolerance may develop to the acute rewarding properties of opioids, and the primary determinants of continued opioid use become the avoidance or termination of drug abstinence (50,64,67,84,131). Heroin is initially sought by human drug users for its incentive motivational properties, which are presumably associated with the high and euphoria experienced after acute administration of the drug (84). However, when allowed chronic unlimited access to opioids, human addicts begin to administer progressively larger doses of opioids and eventually develop a dependence syndrome characterized by the expression of characteristic so-

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matic withdrawal signs with abstinence from opioids (50,84). Furthermore, they begin to report fewer highs and become more concerned with terminating abstinence and avoiding withdrawal (84).

Thus, even in the case of the most studied class of drugs (opioids), an incentive motivational view by itself does not account for the powerful rewarding properties of opioids associated with their ability to alleviate the aversiveness of withdrawal in physically dependent humans and animals (10,56,83,84). We acknowledge that proponents of the incentive view of opioid motivation do not deny that withdrawal is a motivating factor in opioid-dependent animals, but they assert that, in the global phenomenon of opioid addiction, withdrawal plays a secondary role in opioid motivation. Similarly, proponents of the withdrawal view do not dismiss the importance of the rewarding properties of opioids in nondependent animals, but they stress that withdrawal becomes the primary mechanism underlying the motivation for opioids once animals are exposed to opioids. Thus, the idea that opioid motivation stems from the ability of opiates both to elicit incentive reward and to alleviate withdrawal is not new. However, no theory has yet explained when incentive reward or aversive withdrawal becomes more or less important, and how much does reward vs. withdrawal contribute to opioid motivation. For example, could there be some subtle mechanisms of opioid withdrawal in the nondependent state that contribute to opioid motivation? If so, how much is that contribution? At what stage do animals switch from a nondependent to a dependent state? When animals become dependent, does incentive reward still play a primary role? We propose a two-motivational-systems hypothesis of opioid addiction that addresses these questions and helps account for many of the instances of opioid reward that are not explained by contemporary theories of opioid addiction. This proposal has emerged from several studies that were carried out on the neurobiological substrates mediating the motivational effects of opioids (4,5,7,8,10,75). In the following sections, we present the experimental evidence leading to the formulation of our two-motivational-systems hypothesis.

ASSESSMENT OF DRUG MOTIVATION

Because the history of drug intake is an important variable in the study of opioid motivation in the dependent vs. nondependent state, we have employed the place conditioning paradigm. In this paradigm, the rewarding effects of opioids can be demonstrated in nondependent animals after minimal exposure to the drug (71,73,125), thus minimizing the development of dependence/withdrawal effects that result from repeated exposures to opioids. With the same paradigm, animals that have been chronically exposed to opioids still can be assessed for their motivation for opioids in the dependent state.

Many workers in the field on drug motivation assume that the most suitable paradigm for studying drug motivation is the intravenous drug self-administration paradigm. In this respect, we stress the fact that the notion of independent mechanisms underlying the motivation for opioids in the opioid-nondependent vs. the opioid-dependent state would have been difficult to address in the absence of place conditioning and its exquisite temporal control of the pairing of conditioned stimuli with history of drug use (10). Furthermore, given that specific neural manipulations block different classes of motivated behaviors as assessed by place conditioning, it is possible to predict how the same neural manipulations would affect the self-administration of opioids. The discrepancies that result among the different paradigms do not necessarily mean that these paradigms are inherently incompatible. The discrepancies may be the by-product of different states (nondependent vs. dependent and withdrawn) under which animals are tested in the different experimental paradigms.

TERMINOLOGY

In the following sections, we describe the various phases of opioid-seeking by using standard terminology used in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). However, in the Definitions and Predictions section, we reconcile this terminology with our proposed behavioral and neurobilogical criteria, which define similar instances of opioid-seeking in animal models.

In the DSM-IV, *withdrawal* is defined as "a maladaptive behavioral change, with physiological and cognitive concomitants, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance" (DSM-IV, p. 178). In our discussion, we refer to the aversive state associated with this type of withdrawal as the *aversive effects of withdrawal*. When unpleasant withdrawal symptoms and signs develop, the person tends to seek the substance to relieve or avoid those symptoms (DSM-IV, p. 178). We refer to the reward associated with the alleviation of these withdrawal symptoms and signs as the *rewarding effects of withdrawal relief*.

Many investigators have argued that withdrawal can be present after a few injections of opioids or precipitated by an opioid antagonist administered even after a single exposure to an opioid agonist (1,2,22,46,52,66,102,130,137). Because this withdrawal phenomenon is detectable only when using highly sensitive techniques, it is important to distinguish this type of withdrawal from the physical withdrawal signs observed after chronic drug use. Thus, many of the investigators cited earlier have used the term *acute withdrawal*. In our discussion, we have adopted this term to denote the type of withdrawal observed after a few exposures to opioids.

Some individuals show a pattern of compulsive drug use, without any observed signs of tolerance or withdrawal (DSM-IV, p. 178). However, DSM-IV did not provide a specific term for the reward associated with this instance of substance use. To distinguish this type of reward from the reward associated with withdrawal relief, we use the term *acute reward*. Other investigators have used the term *acute* to denote the reinforcing properties of psychoactive drugs during their initial use, i.e., prior to the development of physical withdrawal (54).

The TPP as a Critical Substrate for Acute Reward

Investigations aimed at unraveling the neurobiological substrates underlying the rewarding effects of opioids and other psychoactive drugs have revealed that several neural structures localized or connected to the limbic system of the brain are primary loci for mediating the rewarding properties of these drugs (54,116,133,134). Microinjection studies have revealed that the receptor sites where opioids and stimulants act to produce rewarding effects in drug-naive rats are in the limbic forebrain (i.e., nucleus accumbens and lateral hypothalamus) and midbrain [i.e., ventral tegmental area (VTA) and periacqueductal gray] (3,21,29,93,124,126,135). In addition, electrophysiological studies have indicated that the reward information generated by electrical brain stimulation of these forebrain sites is carried through descending pathways of the medial forebrain bundle (MFB) to the midbrain (12).

Several lines of evidence now suggest that the tegmental pedunculopontine nucleus (TPP) of the midbrain is a critical site for acute reward from opioids (7,75,85,86,88,89). Lesions of the TPP, however, do not interfere with the rewarding effects of withdrawal relief by opioids in dependent and withdrawn animals or with the aversive effects of a withdrawal syndrome in dependent animals (10), both of which are mediated by the same mechanism (4,5,79). We suggest that the TPP-mediated rewarding effects of opioids in the nondependent state are wholly due to the acute rewarding effects of opioids. Anatomical evidence indicates that the TPP region of the midbrain and pons receives neuronal inputs from all the structures identified as sites for eliciting the acute rewarding effects of opioids via direct monosynaptic or indirect multisynaptic pathways traveling through the MFB (120,121). Bilateral ibotenic acid lesions of the TPP region blocked the acquisition, but not retention, of morphine-conditioned place preferences in animals trained with only a few injections of opioids (7,87,89). Nondependent rats that had acquired a morphine-conditioned place preference prior to TPP lesions were capable of retaining and demonstrating these place preferences after lesioning the TPP (7). However, after the lesioned rats were exposed a few times to the same environment, the conditioned preferences were extinguished, and the rats were no longer able to re-acquire the place conditioning with additional injections of morphine (7). These results suggest that TPP lesions block the unconditioned, but not the conditioned, acute rewarding effects of opioids. Similar to ibotenic acid lesions, bilateral electrolytic lesions placed in the midbrain tegmentum [infringing on the ventromedial area of the TPP defined as critical for psychoactive reward (7)] depressed bar pressing for electrical stimulation of the septal region (100,101), the lateral hypothalamus (17) and the MFB (74). The TPP itself has low levels of opioid receptors (45,61), and the effects on the acute rewarding properties of opioids seen after the lesions are most likely due to disruption of an acute reward circuit after the opioid-receptor-bearing neuron. Furthermore, the TPP-induced block of opiate motivation in animals trained with only a few injections of opiates suggests that the TPP region is critical for acute reward in the nondependent state.

Anatomical evidence shows that the TPP is in a position to influence a variety of somatomotor responses because it projects directly to widespread parts of the brainstem reticular formation (69), the thalamus (40,111), the spinal cord (34,111) and the basal ganglia and associated structures (30,48,98,99,115). Furthermore, the TPP region appears to overlap the mesencephalic locomotor region, a region that facilitates locomotion when electrically stimulated in the decerebrate rat (109). Therefore, we hypothesized that the TPP region of the brainstem may serve as an anatomical substrate where acute reward signals generated at more rostral levels of the brain exit the limbic system and gain access to motor systems that initiate behavioral acts (9). However, other evidence using lesions at slightly different TPP loci suggests that TPP lesions can have differential effects on the reward vs. the cataleptic and excitatory locomotor effects of opioids and stimulants (88).

The notion that the TPP region is critical for mediating the acute rewarding effects of opioids (7,10) does not mean that it is also critical for the properties of these drugs, which exert subjective sensory effects (50). In rats, morphine may have distinct cuing or discriminative properties (63). However, these internal cuing effects of morphine were separable from the rewarding effects of the same drug. Combined neural and pharmacological manipulations that blocked the rewarding effects of opioids in nondependent rats did not interfere with the discriminative effects of morphine (63). These results suggest that the discriminative properties of opioids are neurobiologically separable from their TPP-mediated acute rewarding properties. Infusions of morphine into the parabrachial nucleus (PBN), but not into the VTA, serve as stimuli for the acquisition of discrimination learning, whereas infusions of morphine into the VTA, but not into the PBN, produce rewarding effects (49).

Dopamine as a Critical Substrate for the Rewarding Effects of Withdrawal Relief

Lesions of the TPP region provide a tool for disrupting the neural processes responsible for the acute rewarding properties of opioids, thus allowing an independent assessment of the role of withdrawal in opioid motivation in physically dependent animals. In our behavioral assays, we rendered rats physically dependent after chronically exposing them to morphine (60 mg/kg/day for a minimum of 14 days) until they began to show physical signs of a classic withdrawal syndrome (4,5,8,10).

Lesions of the TPP disrupted the acute rewarding effects of opioids in the nondependent state. However, the lesions did not affect the rewarding effects of withdrawal relief in the dependent state (10). Although the TPP region is critical for mediating opioid reward, at least in nondependent rats, there is strong support for the view that the neural function of the neurotransmitter dopamine also is important for opioid reward (13,14,114,135). In opposition to this strong dopaminergic hypothesis, however, is the evidence that opioid reward sometimes can occur when dopamine neuronal function is completely blocked by dopamine antagonists (27,54,59,110). In light of the finding that the TPP lesions separate the acute rewarding effects of opioids in the nondependent state from the rewarding effects of withdrawal relief in the dependent state (10), the effects of dopamine antagonists on the rewarding effects of opioids in nondependent vs. dependent animals were explored (4).

Dopamine antagonists blocked the ability of opioids to elicit reward (withdrawal relief) in dependent rats that were in a state of withdrawal but did not interfere with the ability of opioids to elicit acute reward in nondependent rats (4). Specifically, the conditioned place preferences seen in opioid-dependent and withdrawn rats conditioned with morphine or heroin were blocked by pretreatment with the dopamine antagonist alpha-flupentixol or pimozide. The same conditioned place preferences seen in nondependent rats were blocked by TPP lesions but not by dopamine antagonists (4). Using a modified place conditioning procedure (in which the direct effects of opioids were paired with one environment without the alternate pairing of another environment with the absence of morphine, i.e., withdrawal), opioid-dependent and opioid-nondependent rats acquired preferences for places associated with morphine rather than with unfamiliar neutral places (4). In opioid-dependent rats, the preferences for places paired with the alleviation of withdrawal by morphine were blocked by dopamine antagonists but not by TPP lesions. In nondependent rats, the preferences for places associated with morphine (acute reward) were blocked by TPP lesions but not by dopamine antagonists. We suggest that the dopamine-mediated rewarding effects of opioids in the dependent and withdrawn state are due wholly to the reward associated with the alleviation of aversive withdrawal. Thus, the pattern of effects

produced by dopamine antagonists is exactly opposite to the pattern of effects on opioid reward produced by TPP lesions (4). These results demonstrate a double dissociation of two independent neural systems mediating the rewarding effects of opioids in the nondependent state vs. the dependent and withdrawn state. Only one subclass of rewarding events, those events associated with the presence of an opioid-dependent state and withdrawal, appears to depend on the function of dopamine neurons. Interestingly, similar to the results with TPP lesions in the nondependent state (7), dopamine antagonists appear to block the unconditioned rewarding effects of opioids but not the conditioned rewarding effects previously associated with opioids in dependent rats (65). We suggest that training in extinction (i.e., in the presence of dopamine blockade to prevent unconditioned rewarding effects) is necessary to abolish the conditioned rewarding effects of the dependence system in dependent rats.

Dopamine as a Critical Substrate for the Aversive Effects of Withdrawal

Just as the activation of opioid receptors by morphine in nondependent vs. dependent rats produces different mechanisms of reward, reduced activity on these opioid receptors produces different mechanisms of aversion (5). Opiate antagonists produce clear aversive effects in both morphine-dependent (26,33,41) and morphine-naive (6,73) rats. In morphine-dependent rats, opioid antagonists block exogenous and endogenous opioid activity; in morphine-naive rats, opioid antagonists block only endogenous opioid activity. Dopamine antagonists blocked the avoidance behavior of rats to places previously paired with naloxone-precipitated withdrawal in opioid-dependent rats, but dopamine antagonists did not block the avoidance of places paired with naloxone injected in opioid-naive rats (acute withdrawal) (5). TPP lesions did not interfere with the acute withdrawal effects of naloxone in morphine-naive rats (5). Opiate-dependent and opioid-nondependent rats acquired conditioned aversions for places associated with the absence of morphine (i.e., withdrawal). However, the acquisition of these conditioned aversions depended on the time of deprivation from morphine (5). That is, opioid-dependent rats acquired the aversions if rats were depreived of morphine for 16 or 24 h prior to conditioning. Opiate-nondependent rats acquired the aversions at 11–16 but not at 24 h postmorphine. The aversive effects of withdrawal observed in opioid-dependent rats were blocked by dopamine antagonists (5). The aversive effects of acute withdrawal from a few injections of morphine observed in nondependent rats were not blocked by dopamine antagonists. The results suggest that decreases in the actions of endogenous opioids may give rise to a separate endogenous withdrawal syndrome (acute withdrawal) in nondependent animals (5). It is not clear why the aversive effects of acute withdrawal appear at 11–16 h postmorphine, whereas the aversive effects of chronic withdrawal appear at 16–24 h postmorphine. Nevertheless, the differences in time course between acute and chronic withdrawal further illustrate the differences in the types of withdrawal observed in the nondependent state vs. the dependent state.

In summary, common mechanisms mediate the aversive effects of spontaneous and naloxone-precipitated withdrawal in opioid-dependent rats because both effects are blocked by dopamine antagonists. Common mechanisms also may mediate the aversive effects of spontaneous acute withdrawal and the aversive effects of naloxone in nondependent rats because both effects are insensitive to dopamine antagonist blockade. Although dopamine antagonists block the aversive effects of withdrawal and the rewarding effects of withdrawal relief by opioids in dependent and withdrawn rats, TPP lesions block only the acute rewarding effects of opioids observed in nondependent rats or the acute rewarding effects observed in dependent rats that are not in a state of withdrawal (i.e., rats that received a maintenance dose of morphine, 20 mg/kg, 3.5 h prior to place conditioning with another separate dose of morphine, so that during conditioning these rats do not express aversive effects of withdrawal or rewarding effects of withdrawal relief). TPP lesions, however, do not block the aversive effects of acute withdrawal observed in nondependent rats (5). These results dissociate a single dependence motivational system for the aversive effects of withdrawal and the rewarding effects of withdrawal relief, which is dopamine-mediated, from two other processes: a nondependence system for acute reward that is mediated by TPP and a nondependence system for acute withdrawal that is hypothesized to be mediated by the arcuate nucleus (5,72).

These results support many previous studies that have suggested that acute withdrawal begins with a few or even after a single exposure to opioids (1,2,22,46,52,66,102,130,137). However, these studies have assumed that the phenomenon of acute withdrawal represents the initial stages in the development of a classic withdrawal syndrome. Although some of the symptoms and signs in acute and classic withdrawal may be parts of the same process, we stress that the aversive mechanisms associated with acute withdrawal are fundamentally different from those associated with classic withdrawal. Another line of evidence that supports this idea comes from studies with clonidine. Clonidine (an alpha2-noradrenergic agonist) has been implicated in mechanisms of withdrawal for its properties to alleviate signs of withdrawal in rats (16,123,124) and many of the physical signs and subjective symptoms of withdrawal in humans (31,32,38,51). Therefore, we investigated the effects of clonidine on the rewarding and aversive effects of opioids in the dependent and nondependent states. Using a clonidine dose that has no dopaminergic activity, clonidine blocked the rewarding effects of withdrawal relief by opioids in dependent and withdrawn animals and the aversive effects of spontaneous withdrawal from morphine in dependent and withdrawn animals (79). Clonidine did not block the TPP-mediated acute rewarding effects of morphine or the aversive effects of naloxone in naive rats (presumably the mechanism underlying naloxone aversion in naive rats is analagous to the mechanism underlying acute withdrawal) (79). The results provide an additional line of support for the idea that the aversive mechanisms associated with acute withdrawal are fundamentally different from those associated with classic withdrawal. Furthermore, they suggest that dopaminergic and noradrenergic substrates are linked serially in a neurobiological system mediating the aversive effects of withdrawal and the rewarding effects of withdrawal relief by opioids in the dependent state.

Lack of Tolerance in the TPP Nondependent Reward System: Apparent Tolerance Is Inhibition or Masking of the TPP System

If the reward mechanism of withdrawal relief, which is mediated by dopamine, is dominant in the opioid-dependent state, what happens to the TPP acute reward mechanism in the nondependent state? Based on tissue biochemical changes, tolerance has been though to be the result of long-term cellu-

lar adaptation (23). When dependent rats received withdrawal alleviating doses of morphine (as shown by an absence of somatic withdrawal signs and lack of aversive withdrawal effects that are blocked by dopamine antagonists) 3.5 h prior to place conditioning with morphine, morphine elicited preferences in opioid-dependent rats (no longer in a state of withdrawal) that were blocked by TPP lesions rather than by dopamine antagonists (8). Most important, these TPP-mediated conditioned place preferences now expressed in opioid-dependent (and not withdrawn) rats were equal in magnitude to those expressed in opioid-nondependent rats. Such an abrupt and complete reinstatement of the TPP-mediated acute rewarding effects of opioids suggests that the disappearance of these acute rewarding effects is not due to neural tissue tolerance associated with long-term cellular adaptation after chronic administration of opioids. Rather, the alleviation of withdrawal in dependent rats allows the reexpression of the unaltered neural tissue substrates (the TPP-mediated mechanism) subserving the acute rewarding effects of opioids. Thus, we hypothesize that the behavioral tolerance observed in opioid-dependent rats is due to the inhibition or masking of the acute rewarding effects of opioids (TPP-mediated) by mechanisms associated with opioid dependence and withdrawal. However, the unaltered, TPP-mediated acute rewarding effects that become inhibited or masked by the effects of withdrawal still can play a powerful motivational role, even in dependent animals, once withdrawal is alleviated.

Somatic Signs of Opioid Withdrawal Are Not Synonymous with the Aversiveness of Withdrawal

In animal models of opioid withdrawal, the primary focus has been on the physical aspects of withdrawal (such as somatic withdrawal signs) as indices reflecting the intensity of the aversiveness of withdrawal (11,129). However, animals begin to avoid cues associated with the absence of opioids (i.e., withdrawal) even after they have been exposed to only a few injections of opioids in the absence of any observable signs of withdrawal (5,75). Although we suggest that this early avoidance behavior is associated with fluctuations in endogenous opioid activity (i.e., acute withdrawal and not opioid dependence), we argue that the aversive effects of this acute withdrawal phenomenon are mediated by mechanisms that are different from those of withdrawal in the dependent state. We suggest that at some point this avoidance behavior from acute withdrawal switches to avoidance based on opioid dependence (still at a time prior to the appearance of any signs of somatic withdrawal) (5,75). Therefore, we argue that somatic withdrawal signs are not the most sensitive indices for detecting opioid dependence.

There remains a division in the field as to the appropriate behavioral definition of drug dependence and withdrawal. Some investigators have studied opioid withdrawal in terms of its directly observable physical manifestations (44), and others have studied opioid withdrawal in terms of its properties that produce conditioned avoidance of environments paired with withdrawal (41,62,117). However, Mucha (70) found no predictive relationship between the presence of specific withdrawal signs and the aversive effects of withdrawal as assessed by place conditioning procedures. Furthermore, several other studies have shown that withdrawal aversiveness is induced by the central blockade of opioids (41,55,117) and that the method of place aversion, and not the measurment of the physical signs of withdrawal, is the more sensitive measure of the aversive stimulus properties of opioid withdrawal (41,117). Thus, several lines of evidence now suggest that the somatic signs of opioid withdrawal are not the most reliable indices for predicting the aversive mechanisms that induce conditioned aversive effects (4,5,60,70,117). For instance, rats avoided cues paired with the absence of opioids (i.e., withdrawal) after receiving several injections of high doses of heroin, but these rats did not show any observable signs of somatic withdrawal. This avoidance behavior was blocked by dopamine antagonists in a manner consistent with the block of the withdrawal avoidance behavior of animals chronically treated with opioids (and demonstrating a characteristic somatic withdrawal syndrome) by dopamine antagonists (75). The neurobiological mechanisms subserving the somatic signs vs. the aversiveness of withdrawal must be partly separate because dopamine antagonists blocked the avoidance behavior elicited by spontaneous morphine withdrawal (4) and naloxone precipitated withdrawal (5) in rats chronically treated with morphine (opioid-dependent). The same dopamine antagonist treatments did not attenuate the somatic withdrawal signs associated with the precipitated withdrawal (5). However, clonidine seems to affect both the signs of withdrawal (16,123) and the avoidance of withdrawal in dependent and withdrawn animals (79). Such results illustrate the difficulties in using somatic signs of withdrawal as indices for the motivation of animals to avoid opioid withdrawal (5,70,75). Furthermore, a study that directly compared the effects of somatic signs of withdrawal vs. the aversiveness of withdrawal revealed that the conditioned avoidance of environments associated with opioid withdrawal was the most sensitive behavioral assay of opioid dependence and withdrawal (103).

Withdrawal Aversiveness in the Dependent State Is Mediated by a Patterned Dopaminergic Activity

Data on the aversiveness of opioid withdrawal (4,5,75) with the data presented by Harris and Aston-Jones (44) reveal an interesting dissociation between the dopaminergic mechanisms that mediate the aversive properties of opioid withdrawal and the dopaminergic mechanisms that mediate the somatic signs of withdrawal. Harrris and Aston-Jones (44) showed that systemic alpha-flupentixol precipitated somatic signs of withdrawal in opioid-dependent rats and that the direct dopamine agonist apomorphine reduced the incidence of these somatic withdrawal signs in opioid-dependent and withdrawn rats. These data suggest that decreased dopamine receptor activation mediates the somatic signs of withdrawal. However, pretreatment with the dopamine antagonist alpha-flupenthixol did not reduce the incidence of somatic withdrawal signs in dependent rats that were already showing signs of withdrawal (5). This finding is consistent with the interpretation of Harris and Aston-Jones if one considers that the level of dopamine receptor activation is already depresed in dependent and withdrawn rats. However, these same dopaminergic manipulations had different effects on the aversive effects of opioid withdrawal. Pretreatments with either alpha-flupentixol (4,5) or the direct dopamine agonist apomorphine (77) blocked the acquisition of place aversions to environments associated with opioid withdrawal in dependent animals. Furthermore, pretreatment with the indirect agonist amphetamine, which can both increase the signal-to-ratio of postsynaptic striatal cell activity (42) and potentiate dopamine release from nerve terminals (128), had no effect on the acquisition of conditioned place aversions to environments associated with opioid withdrawal (77).

If the aversive effects of opioid withdrawal in the dependent state were mediated by an absolute decrease in dopamine receptor activation, then both amphetamine and apomorphine would have raised the dopamine receptor activity and decreased the avoidance of places associated with opioid withdrawal. Conversely, if dopamine activity was maximally depressed in opioid-withdrawn rats, then alpha-flupenthixol should not have blocked these aversions. The findings with direct and indirect dopaminergic agonists and antagonists argue that the aversive effects of opioid withdrawal in the dependent state are mediated by a patterned activation of postsynaptic dopamine receptors. Thus, two different dopaminergic mechanisms mediate the somatic and aversive withdrawal properties of opioid withdrawal.

DEFINITIONS AND PREDICTIONS

In the previous sections, we used terms to describe different phases of opioid-seeking that were either defined in the DSM-IV or previously used by investigators in the field. In this section, we attempt to reconcile this terminology with our hypotheses and redefine these terms based on behavioral and biological criteria used in experimental animal models of addiction. Furthermore, we make explicit predictions about the neurobiological substrates of the different phases of opioid-seeking.

Given the evidence presented in the previous sections, we define withdrawal in rats with chronic exposure to opioids in terms of avoidance of cues paired with the absence of opioids (i.e., withdrawal) after at least 16 h of opioid abstinence. We predict that this avoidance behavior is blocked by dopamine antagonists. We define acute withdrawal in terms of avoidance by rats of cues associated with the absence of opioids after 11–16 h of morphine abstinence. We predict that this avoidance behavior is insensitive to blockade by dopamine antagonists (5). However, we define the reward of withdrawal relief in animals chronically exposed to opioids and in a withdrawal state in terms of approach of cues paired with opioids. We predict that this approach behavior is blocked by dopamine antagonists. We define acute reward in terms of the approach of opioid-paired cues in the absence of withdrawal. We predict that this approach behavior is blocked by TPP lesions. Consequently, *opioid dependence* is defined as a state in which aversive withdrawal and the reward of withdrawal relief exist without necessarily being expressed. For example, opioid-dependent animals that have undergone a sufficient number of hours of abstinence from morphine will express aversive effects of withdrawal and rewarding effects of withdrawal relief and therefore are described as opioid dependent and withdrawn. Opiate-dependent rats that have just received opioids for alleviating withdrawal will not express aversive effects of withdrawal or rewarding effects of withdrawal relief and therefore are described as opioid dependent, but not in withdrawal. Conversely, *opioid nondependence* is defined as a state in which withdrawal and withdrawal relief are never present. Animals that are in a nondependent state show only acute rewarding effects. At some point (after a few exposures to opioids), animals may begin to show aversive effects of acute withdrawal. Although these aversive effects of acute withdrawal may be sufficient for opioid-seeking, we believe that they are not necessary for opioid-seeking. In the absence of the TPP, the acute rewarding effects of opioids are never observed (5). However, in the absence of the arcuate nucleus of the hypothalamus (hypothesized to be a critical site for mediating the aversive effects of acute withdrawal), the acute rewarding effects of morphine in nondependent rats are not altered (72).

We admit that these behavioral definitions are somewhat circular in that they partly arose from and depend on neurobiological manipulations to help characterize the putative motivational processes. However, one possible way of breaking the inherent circularity in definitions of motivation is to elucidate the underlying neural mechanisms that support motivated behaviors that are defined based on operational criteria. Once the neural substrates have been identified, one may work back up to behavior and identify those behaviors or aspects of behavior that are affected by manipulations of these sites. Through this interplay between levels of analysis (a type of bootstrapping method), one may eventually arrive at a noncircular behavioral definition of motivation that is not strictly operationally based. Thus, the most parsimonious resolution to this problem would be the identification of a single neural substrate that mediates both the motivational and behavioral expressions of a single intervening variable. This bootstrapping method has already proven valuable in refuting the criticism of triviality. New models of motivation can explicitely separate different types of motivation on both a neurobiological and behavioral level. The existence of separate motivational systems producing different behavioral effects demonstrates that these motivational processes are nontrivial. Thus, an approach based on an interplay between the behavioral and neurobiological levels of analysis could confer the theoretical framework of motivation with greater validity through correlation with physiological and anatomical data. Ignoring Skinner's suggestion that psychologists not physiologize (i.e., define behavioral terms on a neural level), most motivational researchers have looked to neurobiology to evade the problems of motivational concepts being circular and trivial.

THE TWO-MOTIVATIONAL-SYSTEMS HYPOTHESIS

To account for all the different instances of opioid reward and withdrawal discussed thus far, we propose a two-motivational-systems hypothesis for opioid addiction that is based on the distinction between two conditions: an opioid-dependent and an opioid-nondependent state. The motivational mechanisms operating in the two conditions are subserved by independent neurobiological substrates.

We hypothesize that there are two different mechanisms of reward. The first mechanism is best demonstrated in the nondependent state, in the absence of any evidence of dependence and withdrawal. A critical neural substrate subserving this mechanism of reward is the TPP region of the brainstem. In the nondependent state, the primary mechanism underlying the motivation for opioids is their acute rewarding properties. The TPP-mediated reward also is expressed in the opioid-dependent state if animals have just received a withdrawal alleviating dose of opioids and are no longer in a state of withdrawal.

The second reward mechanism is best demonstrated in the opioid-dependent state, in the presence of dependence and withdrawal. A critical substrate subserving this mechanism of reward is dopaminergic neurons. The dopamine-mediated reward is expressed in dependent animals that undergo several hours of deprivation from opioids (at least 16 h) at the same time when the aversive effects of withdrawal are expressed. Thus, in an opioid-dependent and withdrawn state, the primary mechanism underlying the motivation for opioids is the reward associated with the alleviation of withdrawal by opi-

oids. If animals were opioid-dependent but not in a state of withdrawal (i.e., animals had just received opioids for withdrawal relief), then the TPP-mediated reward system (acute reward) becomes the primary motivating factor. After chronic exposure to opioids and the development of opioid dependence, the TPP-mediated reward system does not become tolerant but only inhibited or masked by the mechanisms of withdrawal in opioid dependent rats. Alleviation of withdrawal can unmask the TPP system and reinstate the ability of the TPP to mediate acute reward, even in the opioid-dependent state.

Distinct behavioral mechanisms of withdrawal also exist in the nondependent and dependent states. In the nondependent state, acute withdrawal may develop even after a few injections of opioids. The aversive effects of these acute withdrawal mechanisms are independent of the TPP. The neural substrates subserving the aversive effects of these acute withdrawal mechanisms remain uncertain, but the arcuate nucleus of the hypothalamus is a likely candidate. In the absence of the TPP, we do not know whether these mechanisms of withdrawal can by themselves instigate approach (reward) of opioids. However, the aversive effects of withdrawal from opioids in the dependent state are very significant. These aversive withdrawal mechanisms are mediated by dopamine, and they are inseparable from the rewarding effects of withdrawal relief by opioids. Whenever these aversive withdrawal mechanisms are expressed, the acute reward and acute withdrawal effects of the nondependent state become inhibited or masked. Whenever these aversive withdrawal mechanisms are relieved, the acute rewarding and acute aversive withdrawal effects are reinstated.

Although animals with a chronic history of opioid intake and expressing somatic signs of withdrawal are clearly dependent on opioids, we argue that the motivation associated with opioid dependence develops before any of these somatic signs of withdrawal are detected. We suggest that somatic withdrawal signs are not the best indices of opioid motivation in the dependent state.

CHALLENGES TO THE TWO-MOTIVATIONAL-SYSTEMS HYPOTHESIS

The two-motivational-systems hypothesis rests on the evidence that the TPP region subserves the acute rewarding effects of opioids, whereas dopamine is critical for mediating the rewarding effects of withdrawal relief by opioids. Thus, when nondependent rats prefer an environment associated with morphine rather than a neutral unfamiliar environment, they do so via the TPP-mediated acute reward system. When dependent and withdrawn rats prefer an opioid-associated environment rather than a neutral unfamiliar one, they do so via the dopamine-mediated reward system. Because these two motivational systems are doubly dissociated, one can negate the possibility that the acute and withdrawal relief rewarding effects of opioids reflect a quantitative distinction in the intensity or degree of reward rather than a qualitative distinction between two different kinds of reward.

Given that our hypothesis rests primarily on place conditioning procedures, it is important to rule out some alternate interpretations of the results. In the behavioral assays of opioid withdrawal, opioids are administered to rats in the home cage and saline vehicle in one environment of the place conditioning apparatus, and the avoidance of that environment is later assessed. As such, one can argue that the saline-paired side is most predictive of the absence of opioids. Therefore, spending less time on that side at testing does not necessarily reflect a state of aversiveness and avoidance of the saline-(withdrawal) paired side but rather may reflect the avoidance of stimuli that are exclusively predictive of nonreward (inhibitory conditioning). However, several pieces of data speak against such a possibility. First, when nondependent rats are given a rewarding dose of morphine (2 mg/kg) in the home cage and 21 h later are injected with saline and placed in an environment, the rats fail to acquire an avoidance of the saline-paired side, which is exclusively predictive of the absence of reward (5,10). Second, both nondependent and dependent rats can acquire the avoidance of the saline-paired side, but they do so depending on the time since the last morphine injection during training. That is, 11–16 h of morphine abstinence triggers avoidance in nondependent rats, whereas 16–24 h of abstinence triggers avoidance in dependent rats (5). In both instances, the saline-paired environment is exclusively predictive of the absence of reward. If avoidance of stimuli that predict nonreward is the mechanism underlying this avoidance behavior, then we should not expect different time periods for observing avoidance in nondependent vs. dependent rats. Depending on whether animals had an acute history (nondependent) or a chronic history (dependent) of opioid intake, the avoidance behavior expressed by the rats using exactly the same conditioning procedures is blocked by different neurobiological manipulations (i.e., dopamine antagonists only block the avoidance in dependent rats). If rats were avoiding the withdrawal-paired environment simply because it is predictive of nonreward, then it is difficult to explain why dopamine antagonists block one avoidance behavior but not the other. Therefore, we argue that these aversions reflect two fundamnetally different aversive states of withdrawal associated with opioid dependence and nondependence.

Simple inhibitory conditioning still may explain why nondependent animals avoid a withdrawal-paired side (58,94). That is, the rats will show conditioned avoidance of an environment that predicts a decline in the acute rewarding effects of a previous morphine injection or endogenous opioid activity and not because of the aversiveness of acute withdrawal. More speculatively, a decrease in endogenous opioid activity (induced by naloxone or by acute withdrawal from a few morphine injections) may be the underlying mechanism of inhibitory conditioning. However, because TPP lesions do not block the aversive conditioning effects of naloxone in nondependent rats (5) (and if the mechanisms of naloxone aversion and acute withdrawal in nondependent animals are the same), we suggest that inhibitory conditioning is not the mechanism underlying the conditioned aversions to acute withdrawal. Nevertheless, inhibitory conditioning still can be a possible explanation for the avoidance behavior seen in nondependent animals. However, if TPP lesions do not interfere with the aversive effects of acute withdrawal seen at 11–16 h postmorphine in nondependent rats, then this data would speak more strongly against an inhibitory conditioning mechanism.

Given the two-separate-motivational-systems hypothesis, there are several critical issues that can be raised.

Place Conditioning vs. Self-Administration

Given that our two-motivational-systems hypothesis was derived from place conditioning studies, can this view explain the results of self-administration studies? TPP lesions interfere with the acquisition and initial phase of opioid self-administration [while animals were likely to be in a nondependent

state (89)] but not with the maintenance of opioid self-administration after animals become physically dependent (75). However, if dependent animals are allowed to continue to self-adminster opioids for an extended period of time, then we predict that the TPP-mediated effects would reemerge near the end of long-duration self-administration sessions. Having said that, it is important to note the difference between a dependent animal with a history of only a few heroin injections vs. one with a chronic history. That is, in the case of a dependent animal with history of only a few heroin injections, one or two bar presses may be sufficient to alleviate withdrawal and release the TPP reward system. Accordingly, TPP lesions may interfere with the initial phase of opioid self-administration in animals that have the minimal number of opioid exposures sufficient to render them dependent on opioids (75). In the chronic case, however, it may take many more bar presses to alleviate withdrawal and for the TPP reward system to reemerge.

In contrast to the TPP effects, dopamine antagonists produce the opposite pattern of results. During the acquisition phase of heroin self-administration, the dopamine antagonist haloperidol (0.125–1.125 mg/kg) has no effect on the rewarding effects of heroin (i.e., does not increase or decrease the rate of bar pressing during the first 2 days of heroin self-administration) (127). During the maintenance phase of heroin self-administration, the D1 receptor antagonist SCH 23390 suppresses bar pressing for heroin (below the baseline level) at doses higher than 0.01 mg/kg and in the absence of catalepsy (81). Ettenberg et al. (27) used 0.01, 0.05, 0.1, 0.2 and 0.4 mg/kg of alpha-flupenthixol to block cocaine or heroin self-administration. The 0.05-, 0.1- and 0.2-mg/kg doses increased cocaine self-administration. However, 0.2- and 0.4-, but not 0.1-, mg/kg doses decreased heroin self-administration below the saline injection level. Motoric effects, at least at the 0.2-mg/kg dose, are ruled out because the same dose produced an increase in cocaine responding. Thus, two studies with different dopamine antagonists have shown that dopamine antagonists suppress heroin self-administration below the baseline level in the absence of cataleptic effects. It is conventional to assume that a reduction in reward produces an increase in the rate of bar pressing, presumably because the animal has to self-administer more to compensate for the reduced reward, but what does a dopamine-antagonist-induced decrease in heroin self-administration mean? Does it mean that the dopamine antagonist had no effects on heroin reward, as suggested by Ettenberg et al. (27)? Or could it mean that dopamine antagonists completely blocked the rewarding effects of withdrawal relief by heroin so that animals were no longer motivated to approach cues (i.e., the bar) associated with the alleviation of withdrawal? We argue that the latter is an equally likely explanation.

Another challenging question is why selective lesions of the dopamine terminals in the nucleus accumbens with 6-hydroxydopamine (6-OHDA) microinjections (92) did not block the maintenance of heroin self-adminstration. We suggest that these results cannot exclude a role for dopamine in opioid reward. The nucleus accumbens dopamine is not the only dopamine link supporting heroin self-administration in the dependent state, and lesioning this dopamine link by itself is not sufficient to block heroin self-administration. Evidence exists for other dopamine projections from the midbrain to, e.g., the visceral (agranular insular) cortex, which play a role in the motivational mechanisms of opioids (139). These alternate projections may be sufficient to support the mechanisms of opioid self-administration in the dependent and withdrawn state.

Dopamine and Opioid Reward

Previous studies have shown that dopamine antagonists block the acquisition of conditioned place preferences to places paired with heroin (13,114) or with morphine (107,108). Given the short-term history of exposure to opioids in these studies, how do we explain these findings in terms of our proposed hypothesis? In an explicit study of this issue using heroin, Nader et al. (75) demonstrated that just a few injections of high doses of heroin, such as those used in the studies of Bozarth and Wise (13) and Spyraki et al. (114), can induce an opioid-dependence state in the absence of any observable signs of somatic withdrawal. This finding could explain the dopamine-antagonist-induced block of the preferences produced by the very high doses of heroin used in these studies. However, Shippenberg and Herz (107,108) showed that chronic D1 antagonism with the compound SCH 23390 blocks the acquisition of a place preference to an environment paired with a few low doses of morphine (i.e., a nondependent state). Nevertheless, there are confounding aspects in these results. In control experiments, acute injections of SCH 23390 were used to assess the motivational effects the antagonist had on its own; in the primary experiments, chronic continuous exposure to SCH 23390 delivered by minipumps was used to block the conditioned place preferences for morphine (107,108). Most important, even in the control experiments, when the acute dose of SCH 23390 was 100 times lower than the daily rate of SCH 23390 delivery through the minipumps, the acute dose still produced a robust conditioned place aversion in drug-naive rats (107,108). Thus, when using minipumps with 100 times higher doses of SCH 23390, it is quite possible that the behavioral aversion produced by SCH 23390 was so great as to render the pharmacologically intact rewarding effects of low doses of morphine completely ineffective in supporting place preferences.

Unfortunately, the one place conditioning study that used acute as opposed to chronic SCH 23390 to challenge the acquisition of low-dose morphine place preferences (57) made use of a biased place conditioning protocol in which rats were consistently conditioned to their least preferred side. Effects in biased place conditioning procedures are subject to alternative interpretations in terms of stress, anxiety and other nonspecific effects (20,125). In a later counterbalanced, unbiased place conditioning paradigm, 6-OHDA lesions of (or unilateral microinjections of SCH 23390) into the nucleus accumbens blocked the acquisition of morphine place preferences in previously drug-naive rats (106). These findings are surprising, given that the 6-OHDA treatment resulted in only a 46% depletion of dopamine in the nucleus. Lesions of the mesolimbic dopaminergic system system that result in $<90\%$ dopamine depletion often do not cause significant behavioral changes (95,119). In fact, 6-OHDA lesions of the accumbens that resulted in approximately 75% decrease in nucleus accumbens dopamine levels had no effect on amphetamine place preferences (113). It is also suprising that unilateral blockade of dopaminergic receptors in the nucleus accumbens with SCH 23390 should completely block the acquisition of systemic morphine place preferences (106). Rather, if half of the rewarding properties produced by systemic morphine are working through the contralateral nucleus accumbens, then only an attenuation of conditioned preferences for the mor-

phine-paired environments should be seen. At present, it is difficult to reconcile the cited experiments with our demonstration that dopamine antagonists (alpha-flupentixol) at a pretreatment time that has been shown to have no motivational effects and at a dose that blocks both D1 and D2 receptors (104) has no effect on the acquisition of a preference for an environment paired with even a low dose (2 mg/kg intraperitoneally) of morphine (4).

There remain other questions for which clear answers are not yet available. First, opioids microinjected into the VTA produce conditioned place preferences in nondependent animals (21,29,93,124,135). If VTA–dopamine neurons do not mediate these preferences, as our hypothesis predicts, then what mediates this acute VTA–morphine reward? We suggest that the reward signals generated by opioids microinjected into the VTA activate nondoapaminergic projections to the TPP in the nondependent state. Evidence shows that the conditioned place preferences produced by morphine microinjected into the VTA in nondependent animals are not blocked by systemic dopamine antagonists but are blocked by TPP lesions. However, dopamine antagonists block the acquisition of conditioned preferences for morphine microinjected into the VTA when animals are in an opioid-dependent and withdrawn state (78,80). Second, opioids microinjected into the nucleus accumbens produce conditioned place preferences in nondependent rats (29,124,126). Even so, when animals are chronically exposed to opioids, the microinjection of opioid antagonists into the accumbens produces withdrawal aversions (41,55,117). If the neural systems mediating acute reward in nondependent animals and the reward of withdrawal relief in dependent animals are separate, then why is the same neural region (accumbens) involved in both the acute rewarding and the aversive withdrawal effects of opioids? Although we do not have experimental evidence to answer this question, we hypothesize that, similar to the findings with microinjections into the VTA, the reward signals generated by opioids microinjected into the accumbens activate descending projections to the TPP in the nondependent state. However, after chronic exposure to opioids, a separate population of opiate receptors within the accumbens that are associated with dopamine terminals projecting from the VTA become the primary substrate mediating the withdrawal motivational effects of opioids. Thus, we predict that the conditioned place preferences produced by opioids microinjected into the accumbens in previously drug-naive animals will be blocked by TPP lesions and not by dopamine antagonists. However, the conditioned place preferences produced by the same microinjections of opioids into the accumbens will be blocked by dopamine antagonists and not by TPP lesions in opiate-dependent and withdrawn animals. One may wonder why lesions of the TPP region would block the acquisition of opioid place preference, if the opioid reward signals were generated at more rostral sites. Our hypothesis implies that the reward signals of opioids in the nondependent state are generated in multiple rostral regions of the limbic system but that they converge to exit the limbic system through the TPP region of the brainstem.

RELEVANCE TO HUMAN ADDICTION

The two-motivational-systems hypothesis proposes that independent motivational systems mediate the rewarding effects of opioids in the nondependent state and in the physically dependent/withdrawal state. In the opioid-dependent state and during opioid withdrawal, the rewarding effects of withdrawal relief inhibit or mask the acute rewarding effects initially exerted in the nondependent state, but the acute rewarding effects are unmasked after the alleviation of withdrawal. Thus, when human drug users are given unlimited access to drugs, the termination of abstinence can unmask the TPP acute reward system, thus independently leading to a further escalation in motivation for opioids (8). In the following sections, we discuss the relevance of this hypothesis to findings in human addicts as they relate to systems of reward and aversive withdrawal.

Reward Systems

The two-motivational-systems hypothesis can explain the findings in human opioid users. As Goldstein (35) described the typical history of hard-core addicts, "sometimes in adolescence, heroin is tried in social setting, at the urging of friends. This usually occurs more out of curiosity and thrill-seeking than in response to a stressful life situation, although escape from stress, anxiety, or intolarable conditions of life can be important factors facilitating repeated heroin use in the early stage." Thus, typical beginning heroin users (with little tolerance) start by injecting themselves repeatedly, striving to be as high as possible (25). We suggest that this phase of heroin-seeking is analogous to the TPP-mediated acute reward in nondependent rats. After repeated heroin use (perhaps a few days or a week), the user develops tolerance to the drug, and the amount of heroin injected becomes insufficient to achieve a high (25). At this point, when the user is sick due to withdrawal, he becomes in desperate need for heroin to alleviate withdrawal (25). The clinical observations indicate that the majority of addicts say that they are currently using heroin to get rid of problems such as withdrawal and stress (35,36,84). These observations are consistent with our view that, when physical dependence develops and withdrawal is present, the TPP system becomes inhibited or masked by the dependence system. When withdrawal is alleviated and the heroin user is stabilized on methadone, he becomes protected against withdrawal, which in the past had forced him to seek withdrawal relief with heroin (24,25). However, once the heroin user is on methadone and withdrawal is alleviated, the heroin user continues to seek opioids and nonopioid drugs (118), presumably to achieve a high. This finding is a prediction of our hypothesis that once withdrawal is alleviated, the TPP system reemerges and leads to a further escalation in motivation for opioids. We acknowledge that most heroin users stabilized on methadone for long periods of time stop completely to use heroin. However, we also point to the fact that in the majority of cases reported in Canada, addicts do not stay on methadone for long periods of time, and they go back to their heroin habit within 6 months after stopping an apparently successful treatment (90,91).

We caution that the neural mechanisms subserving the subjective sensory experience of highs and euphoria are not synonymous with the neural systems subserving the motivation to seek drugs. Evidence shows that the sensory discriminative effects and the motivational effects of opioids are processed separately and that one can disrupt one system but not the other (49,63). However, because the discriminative effects and motivational effects elicited by opioids always occur at the same time, they begin to predict one another because of their learned association over time (63,76,80). Therefore, when humans seek opioids to get high, we suggest that this

seeking is due to the sensory cues of the high, which exert powerful conditioned motivational effects. As long as the system mediating the subjective effects of the high and the motivational system that drives the individual to seek the drug are both intact, it is difficult to tell the effects of the discrimination and motivation systems apart. However, just as in animals (49,63,97), if the motivational system is selectively disrupted, then the high and euphoria still can be experienced, but the conditioned motivational effects of this sensation would extinguish over time and lose their motivational power. In other words, the addict will no longer be motivated to seek more drugs. An example that illustrates the dissociation between discriminative sensation and motivation in humans is the administration of morphine to relieve pain in patients. In the absence of morphine, the patient experiences pain, but at the same time the patient is motivated to avoid the source of pain. In the presence of morphine, motivation gets disrupted, so that the subjective experience of pain can still be felt, but the patient is no longer motivated to do anything about it. In this line of reasoning, we assume that the subjective feeling of being high is coactive with the TPP acute reward system, whereas the sensory experience of feeling straight (after withdrawal relief) is coactive with the dopamine withdrawal relief system. It is the activation of the motivational systems and not the sensory discrimination systems that instigate drug-seeking. However, it is difficult for humans to make this distinction because (we argue) unconditioned motivation itself is not subjectively accessible. Therefore, humans report that they seek drugs to get high simply because this subjective sensory experience acquires over time very powerful conditioned rewarding effects.

Withdrawal Systems

The two-motivational-systems hypothesis is based on the assumption that there are two separate mechanisms for withdrawal: acute withdrawal observed in the nondependent and dependent states at 11–16 h postmorphine in rats and classic withdrawal observed only in the dependent state at 16–24 h postmorphine in rats. These time frames for detecting withdrawal differ from those observed in humans. For example, time course studies in nondependent human volunteers that looked at the naloxone-precipitated effects after a single morphine dose found that the most intense subjective withdrawal symptoms appear at 6 h after morphine administration (52). Hoever, more severe physical signs and subjective symptoms of classic withdrawal in dependent humans were not reported until at least 9 h postmorphine (51). Variations such as dose, schedule of administration, metabolism and species differences may explain why these time frames in the rat model do not match exactly those in humans. However, there is an important consistency between the two lines of studies in that the aversiveness of acute withdrawal appears prior to the severe aversiveness of classic withdrawal. The point at which the transition from nondependence to dependence occurs is not known, but studies that have addressed this issue in humans found that there is a time window during which repeated opioid administrations result in escalation to physical dependence (53). In other words, if opioid exposures are widely spaced in time, multiple exposures may have no greater effects than a single exposure (53). These results suggest that opioids can be sought for a long period of time through a nondependence motivational system if exposures are spaced, without necessarily involving a dependence motivational system.

It is important to sort out the relationship between the withdrawal avoidance in rats and the physical signs and subjective symptoms of discomfort reported by humans during withdrawal. In a previous section, we argued that the physical signs of withdrawal are not synonymous with the aversiveness of withdrawal. Although we mentioned previously that clonidine may not be a useful tool in drawing a distinction between somatic signs and avoidance of withdrawal in experimental animals (because it blocks both phenomena), human studies have found that clonidine exerts differential effects on the objective autonomic and physical signs vs. the subjective report of discomfort from morphine withdrawal (31,51). Together, the animal and human findings help illustrate one main point, that the mechanisms underlying the physical signs of withdrawal and the aversiveness of withdrawal are not the samem but the remaining question is whether the subjective symptoms of morphine withdrawal in humans and the motivation to avoid withdrawal or seek relief are synonymous. So far, we have not obtained any evidence in experimental animals that addresses this question directly. However, from what is known about the neural mechanisms subserving the discriminative and rewarding effects of opioids, we hypothesize that an analogous scenario applies to the discriminative and aversive effects of opioid withdrawal. In other words, the subjective sensory experiences of pain and discomfort from withdrawal acquire a motivational power only through association with patterned motivational activity in the dopaminergic withdrawal system. Thus, the addict is seen as motivated to avoid the pain and discomfort of withdrawal or has a great desire to seek relief. We suggest that this motivation is only because these two subjective experiences of withdrawal aversiveness and withdrawal relief are associated with changes in activity in the dopaminergic motivational system. If this dopaminergic motivational system is interrupted, then the subjective pain of withdrawal or the feeling of withdrawal relief may still be present, but the addict will no longer be motivated to avoid withdrawal or seek relief.

Unlike the aversive withdrawal and reward systems in the dpendent state that, we suggest, involve the same neural substrate (dopamine), the two-motivational-systems hypothesis proposes that the systems mediating acute withdrawal and acute reward in the nondependent state are separate. Although indirect evidence suggests that acute withdrawal is not necessary for opioid-seeking [i.e., lesions of the arcuate nucleus do not block morphine conditioned place preference in nondependent rats (72)], we still do not know whether acute withdrawal is sufficient for opioid-seeking. Thus, the subjective experience of disphoria reported by nondependent humans in acute withdrawal may still come to serve as learned conditioned sensory cues sufficient for driving an individual to seek opioids. However, this sensory experience is not necessary for nor is it related to the neurobiological mechanisms by which humans seek opioids for highs and acute rewarding effects.

An important question arising from our two-motivational-systems hypothesis is that, as dopamine antagonists block the rewarding effects of opioids in the dependent and withdrawn state, why do schizophrenic opioid addicts on neuroleptics continue to self-administer heroin? We argue that neuroleptics interfere only with the reward process associated with the alleviation of withdrawal. In other words, neuroleptics will block the motivation to seek relief only if schizophrenics were in a state of severe withdrawal. Although we cannot be precise, we assume that many of these schizophrenic addicts are not in a state of withdrawal, perhaps because they are nonde-

pendent, they were detoxified before hospitalization or they are maintained on opioid medication to control withdrawal. As such, our hypothesis predicts that once withdrawal is alleviated, the TPP acute reward system reemerges and leads to an escalation in opioid-seeking. Thus, in schizophrenic opioid addicts, we predict that neuroleptics may render the addict less motivated to seek withdrawal relief only if he were in a state of withdrawal. Otherwise, the acute rewarding effects of heroin are unmasked, and schizophrenics will seek heroin for its acute rewarding effects, despite the neuroleptic blockade. We also note that indirect evidence from animal studies (65) suggests that neuroleptics may not block the conditioned rewarding effects of withdrawal relief but rather the unconditioned rewarding effects. This suggestion means that, even if some schizophrenics were in a state of withdrawal, neuroleptics will not initially block the motivation for opioids completely. Some conditioned approach to opioids may persist until extinction in the schizophrenics. If the amount of opioids taken during the time before extinction is enough to alleviate withdrawal and switch to the nondependent state, then we predict that the TPP system becomes active again and thus drives the schizophrenics to seek more opioids, despite the neuroleptic medication.

CRITIQUE OF PREVIOUS VIEWS OF ADDICTION

Although several interesting views of addiction have been presented over recent years (54,97,116,135), the two opposite positions presented by Koob and Bloom (54) and Wise and Bozarth (135) serve to summarize the divisions in the field regarding the primary mechanisms responsible for instigating drug use. The view proposed by Koob and Bloom (54) is an opponent process (withdrawal/dependence) theory of addiction. Opponent process theory supposes that the nervous system is organized such that rewarding drug stimuli activate rewarding processes that are opposed by aversive processes in a simple dynamic control system (54,112). Activation of the reward processes is hypothesized to follow the drug injection closely. In contrast, the opponent aversive processes are hypothesized to build up in strength slowly as a function of repeated exposures to the drug and to decay slowly. Thus, in the presence of the drug, these aversive processes have relatively weak effects. After repeated drug exposure (but in the absence of the drug), these opposing aversive processes become stronger. Koob and Bloom (54) postulated that the aversive effects of drug withdrawal eventually become the prime instigators of drug motivation because of the need to alleviate the withdrawal resultant from previous drug use.

The view of Wise and Bozarth (135) is an incentive (psychomotor stimulant) based theory of addiction. This theory stresses that drug similar states rather than drug opponent or withdrawal states as the most powerful stimuli for drug use [drug use can occur through activation of the mesolimbic dopamine system, independent of the presence of any condition of withdrawal (135)]. Chronic opioid use can lead to a withdrawal syndrome. However, withdrawal only accentuates (116) or sensitizes (97) the initial incentive effects produced by opioids (135).

At the level of behavioral description, the place conditioning data support a withdrawal/opponent process model of motivation. An opioid reward effect and an aversive (presumably opponent) withdrawal effect were seen in both opioid-nondependent and opioid-dependent animals (4,5). However, at the process (i.e., incentive vs. opponent process) and the neural (i.e., dopamine vs. TPP) levels of analysis, the data are inconsistent with both the incentive and opponent process views. Several lines of evidence are inconsistent with the opponent process explanation of opioid motivation. In the opponent process view proposed by Koob and Bloom (54), two possible neurobiological mechanisms could support the opponent process. The first is a within-system opponent process in which the primary cellular mechanism activated by the drug itself becomes tolerant, thus allowing the opponent aversive process (within the same neural system) to be expressed when unopposed by the drug. The second is a between-systems opponent process in which the initial reward process causes activation of a separate neural system underlying the opponent aversive process (54). Pivotal to all theories of opponent process is the proposition that the aversive processes are triggered by (and thereby completely reliant on) the presence of an initial reward process. Thus, in the absence of the initial reward process, there could be no secondary opponent or aversive process. However, TPP lesions that blocked the initial acute rewarding effects of morphine in nondependent rats did not interfere with the normal development of aversive withdrawal processes (hypothesized to be opponent and dependent on the primary rewarding process), such as the withdrawal aversions seen in dependent rats and the naloxone aversions (or spontaneous withdrawal aversions from acute morphine injections) observed in nondependent rats (5,10). These findings are inconsistent with the core assumption of opponent theories of drug-seeking behavior because the mechanisms mediating the induction of dependence and withdrawal are independent of the mechanisms mediating acute reward. Second, although the aversiveness of withdrawal may be critical for opioid motivation in opioid-dependent rats [because dopamine antagonists block the aversiveness of withdrawal and the rewarding effects of withdrawal relief by morphine (4)], a similar withdrawal phenomenon [i.e., naloxone or acute withdrawal after a few morphine injections (5)] in nondependent rats is not necessary (although it might be sufficient) for the rewarding effects of morphine [because arcuate nucleus lesions block the aversive effects of naloxone without interfering with the acute rewarding properties of morphine in nondependent rats (72)]. Third, although both reward and withdrawal effects are observed in nondependent and dependent animals (5,8), these reward/withdrawal processes in the nondependent vs. the dependent states depend on different neural substrates (5), thus questioning the notion that the same neural circuit mediating initial drug reward (acute reward) comes to serve as the substrate for withdrawal alleviation in the dependent state (54).

Several lines of evidence also are inconsistent with the incentive/psychostimulant view of opioid motivation. First, two independent mechanisms mediate the incentive effects of opioids in nondependent (TPP) and opioid-dependent (dopamine) animals (4). Moreover, our data suggest that only one of these processes is dominant at any one time. Although the incentive/psychostimulant view acknowledges the existence of separate reward (positive reinforcement) and withdrawal-relief (negative reinforcement) mechanisms, this theory posits that both mechanisms are concurrently active. We suggest that this discrepancy between models is due to the fact that the incentive/psychostimulant model defines withdrawal in terms of somatic withdrawal signs, which are separate from the aversive effects of withdrawal. Second, withdrawal does not result in sensitization of the acute incentive effects (TPP) of opioids. On the contrary, withdrawal prevents the expression of these TPP-mediated incentive effects (8). Third, the findings that all of the rewarding effects of morphine in de-

pendent and withdrawn rats are due to withdrawal relief (4,79) question the premises of the incentive/psychomotor stimulant views of addiction by stressing that withdrawal is not important for drug reward and that drug-similar (rather than withdrawal or drug-opponent) states can account for all instances of drug-seeking.

At the neural level, proponents of the incentive and the withdrawal/opponent process views ascribe a critical role for the dopaminergic VTA projection to the nucleus accumbens in the rewarding effects of psychoactive drugs (54,97,116,135). In turn, it has been proposed that the nucleus accumbens acts as a limbic-motor integrator that converts reward into action (68) and that, through reciprocal interactions with the amygdala, stimulus-reward associations are formed (18,28,47). One main difference, however, is that the incentive view asserts that the dopaminergic projection to the accumbens is critical for opioid and stimulant (cocaine/amphetamine) rewards, whereas opponent process proponents (54) suggest a critical role for dopaminergic projections in stimulant reward and for the nondopaminergic projection from the accumbens to the ventral pallidum in opioid reward. However, this opponent process view does not explain why excitatory amino acid lesions of the nucleus accumbens do not block the conditioned place preferences produced by morphine in nondependent animals (85,87), nor does it explain why dopamine antagonists block opioid reward selectively in dependent animals (4). Similarly, the psychostimulant view does not explain why dopamine antagonists has no effect on the rewarding effects of heroin during the initial acquisition of heroin self-administration (127), nor it does explain why the blockade of dopamine function does not block morphine-conditioned place preference in nondependent animals (4,75). Thus, a single VTA–accumbens–pallidal circuitry cannot accommodate the findings that opioids elicit rewarding effects through activation of two mechanisms in the brain: one through the TPP subserving the acute rewarding effects of opioids in the nondependent state and a separate dopamine-mediated circuitry subserving the rewarding effects of withdrawal relief by opioids in the dependent state.

IMPLICATIONS FOR THE DEVELOPMENT OF POSSIBLE PHARMACOTHERAPIES FOR OPIOID ADDICTION

One of the hopes from studies of the neurobiological bases of opioid addiction is the rational outline of pharmacotherapeutic strategies for breaking the cycle of addiction. From the opponent process view of addiction, one infers that the most effective strategy would be the interference with the opponent (withdrawal) process. Conversely, from the incentive view, one infers that the best strategy would be the interference with the process that mediates acute reward. Obviously, our position is that both withdrawal and acute reward processes must be interrupted to block opioid-seeking. Our data suggest that dopamine antagonists interfere with the withdrawal and withdrawal-relief processes of the dependence system. So far, our studies have not addressed the issue of interfering with acute withdrawal. In the following paragraphs, we discuss potential strategies for interfering with acute reward.

Interestingly, a recent study has uncovered two separate mechanisms for cocaine-seeking (105) that are reminiscent of the two-opioid motivational mechanisms we propose in this review, i.e., a D1-receptor system that provides a sense of gratification (perhaps analogous to the withdrawal-relief system) and a D2-receptor system that triggers an escalation in drug-seeking (perhaps analogous to the TPP acute reward system). Although, our review does not address the neural systems involved in cocaine-seeking or how these systems relate to opioid-seeking, there are conceptual parallels between the two studies that deserve attention. Self et al. (105) suggested that a good approach to block drug-seeking behavior is to stimulate the D1-receptor system with agonists, in the hope of providing gratification in cocaine-dependent humans without triggering a drive to seek more cocaine (82). Given the parallel between cocaine and opioids in having a withdrawal-relief-like system and an acute-reward-like system (irrespective of the neural substrates subserving these reward systems), we predict that activation of the withdrawal-relief system will lead to gratification while unmasking the acute reward system and thus trigger a new drive to seek cocaine.

Thus, in addition to the blockade of the withdrawal-induced mechanisms of opioid-seeking, it will be necessary to devise pharmacotherapeutic strategies that selectively interfere with the acute rewarding effects of opioids. However, the question is which part of the acute reward circuitry should be targeted for disruption? Drugs that block opioid action, either by preventing opioids from binding to the receptor (i.e., antagonists) or perhaps by interfering with the transfer of the opioid signal from the receptor to the cell, are problematic for two reasons. First, although this strategy blocks both the dependent and nondependent motivational systems, the opiate addict will not comply with such a strategy because receptor blockade precipitates a withdrawal syndrome. Second, even if withdrawal was completely absent, the addict will not comply with an opiate-receptor-blockade strategy because the blockade also will block the discriminative opioid effects (i.e., the high). Although experimental evidence reveals that the discriminative effects of opioids are separate from their motivational effects (which energize the seeking of opioids), the close association of discriminative and motivational effects render the sensory experience of the high as a very powerful positive cue in opioid-seeking. Thus, when an opioid-blocking drug prevents the experience of a high, the addict will be motivated to avoid such a drug and not comply with the therapy. In support of this argument is the observation that it is difficult to persuade heroin addicts to take naltrexone for the control of dependence (36,37). Therefore, we suggest that an effective strategy would be to interrupt the acute reward system at a point several synapses after the opioid-receptor-bearing neurons, i.e., after the mechanisms mediating the motivational and discriminative effects of opioids become separate. The TPP region is an ideal site for making this interruption because lesioning the TPP does not affect the withdrawal mechanisms of opioids, nor does it interfere with the discriminative effects of opioids. As such, we speculate that an addict may comply with taking a drug that blocks neurotransmission in the TPP region because the drug will not precipitate any form of withdrawal and should not interfere with getting high. However, once the TPP is blocked, the conditioned motivational effects of the high will extinguish over time. Ultimately, the addict can still experience the high from opioids. However, this sensory experience will lose its motivational power through extinction, and the addict will be no longer motivated to seek more highs and more opioids.

CONCLUSION

The two-motivational-systems hypothesis for opioids also may help explain the motivational effects of nonopioid stimuli in so far as these motivational effects produced by these other stimuli also obey a boundary between deprivation and non-

deprivation states (76). Dopamine antagonists block the rewarding effects of food in food-deprived (133,136) but not in food-sated (4) rats. These findings are the mirror image of the TPP lesion results showing a blockade of the rewarding effects of food in sated but not in food-deprived rats (10). Similarly, TPP lesions do not interfere with food self-administration during the initial phase of a progressive ratio schedule (96), presumably when animals are still in a state of food deprivation. The same lesions, however, strongly interfere with food self-administration during the later phase of the progressive ratio schedule (96), presumably after animals have eaten enough food pellets to alleviate hunger and switch to a nondeprivation state. Robertson et al. (96) provided a learning and memory (rather than a motivational) interpretation for these data, but their results also are consistent with a two-motivational-system interpretation. Given the similar behavioral patterns dependent on deprivation state with both opioids and food and the analagous effects of TPP lesions and dopamine antagonists in both the opioid and food motivational systems, the results are consistent with the notion that opioids may directly activate the neural processes that evolved to subserve natural motivation (116,133).

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APPENDIX

Table 1 summarizes results from place conditioning experiments. Three different place conditioning procedures were used. The B procedure (standard place conditioning with exposure to both environments) involved exposing rats to the unconditioned stimulus (US) in one environment (environment-US) for a 1-h period. On another day, the rats were exposed to the other environment in which the US was absent (environment-no US). These place pairings were alternated for a total of four pairings in each of the two environments spread over an 8-day period. Thus, animals conditioned with morphine as the US received four environment-morphine and four environment-saline sessions. On the test day, rats were given free access to both environments, and the times spent on each side during a 10-min test period were recorded. Two modified versions of the B procedure were employed to distinguish the relative contributions of the environment-US and environment-no US pairings to the final behavior of the animals. In the single-side-reward procedure (previously referred to as the M procedure in the case of opioids and the F procedure in the case of food), rats received only the four environment-US sessions over the same 8-day period. On alternate days, instead of receiving environment-no US training sessions, rats were kept in their home cages. On the test day, rats had a choice between an environment paired with the US and a neutral environment. In the single-side-aversion procedure (previously referred to as the W procedure in the case of opioids and the H procedure in the case of food), rats received the four environment-no US training sessions over an 8-day period. On alternate days, the rats were exposed to the US in their home cage. Using morphine as an example, animals would receive four environment-saline training sessions over an 8-day period. On the intervening days, rats were given a morphine injection in their home cage.

Table 1 also describes manipulation of another variable, the state under which animals were conditioned. With regard to morphine and food, rats conditioned in a nondeprived state were drug-naive or food-sated, respectively. When conditioned in a deprived motivational state, animals were made morphine-deprived by administering three injections of 20 mg/kg/day for 2 weeks and conditioned 24 h after the last morphine injection. Similarly, animals trained in a state of food deprivation were conditioned after 22 h of food deprivation. In the case of heroin, there was no pretreatment with opioids because the high 0.5-mg/kg dose used for conditioning in itself was sufficient to induce a deprived motivational state.

Table 1 also describes place conditioning in rats treated with a dopamine antagonist (alpha-flupentixol) or that had bilateral sham or ibotenic acid lesions of the TPP nucleus. A 0.8-mg/kg intraperitoneal dose of alpha-flupentixol was administered 2.5 h prior to each conditioning session. We previously reported that, at this dose and pretreatment time, alpha-flupentixol does not possess any unconditioned motivational properties on its own (43,59).

TABLE 1
RESULTS OF PLACE CONDITIONING

	B Procedure	Single-Side Reward	Single-Side Aversion
Results using Morphine			
Nondeprived rats, previously drug naive			
Sham lesions	Preference	Preference	No preference or aversion (24 h after last injection)
TPP lesions	Blocked	Blocked	—
Neuroleptic pretreatment	Preference	Preference	—
Deprived rats, at least 2 weeks of 60 mg/kg/day morphine and conditioned 24 h after the last morphine injection			
Sham lesions	Preference	Preference	Aversion
TPP lesions	Preference	Preference	Aversion
Neuroleptic pretreatment	Blocked	Blocked	Blocked
Results using Heroin			
Nondeprived rats, conditions with 0.05-mg/kg dose			
Sham lesions	Preference	Preference	No preference or aversion
TPP lesions	Blocked	Blocked	—
Neuroleptic pretreatment	Preference	Preference	—
Deprived rats, conditioned with 0.5-mg/kg dose			
Sham lesions	Preference	Preference	Aversion
TPP lesions	Preference	Preference	Not tested
Neuroleptic pretreatment	Blocked	Blocked	Not tested
Results using Food			
Nondeprived rats, food-sated			
Sham lesions	Preference	Preference	No preference or aversion
TPP lesions	Blocked	Blocked	—
Neuroleptic pretreatment	Preference	Preference	—
Deprived rats, deprived of food for 22 h			
Sham lesions	Preference	Preference	Aversion
TPP lesions	Preference	Preference	Aversion
Neuroleptic pretreatment	Blocked	Not tested	Blocked