EFFECT OF STRESS ON OPIOID-SEEKING BEHAVIOR: EVIDENCE FROM STUDIES WITH RATS[1,2]

Yavin Shaham, Ph.D.
Addiction Research Foundation

ABSTRACT

Studies concerned with the relation between exposure to stress and the behavioral effects of opioid agonists in animal models of drug use are reviewed. These studies, which primarily utilized male rats, indicate that under certain conditions short-term mild stressors increase self-administration of opioid drugs and reinstate heroin-seeking behavior following a drug-free period. On the other hand, there is evidence that long-term chronic inescapable stressors and severe acute stressors reduce the reinforcing effects of morphine as measured by a conditioned place preference procedure and decrease the behavioral effects of other positive reinforcers. The results of the studies reviewed suggest that stressors are important modulators of opioid-taking behavior, especially during drug-free periods. The implications of these findings to the understanding of the neurobiology of relapse to opioid-seeking behavior and for strategies for medication development to prevent relapse to heroin are discussed.

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INTRODUCTION

Stress is thought to be involved in the development of psychiatric and health disorders (1). Opioid users usually report a high incidence of aversive life events, and based on these self-reports it has been suggested that stress is an important factor in the etiology of drug abuse (see 2,3). However, studies in humans that have examined the effect of stress on opioid use are correlational; they rely on retrospective self-reports of stress and often on self-reports of illegal drug use. Thus, it is difficult to draw conclusions about a link between stress and opioid use (see 4,5).

Because of the methodological and ethical considerations of research with humans, it may be more suitable to examine the effect of stress on drug-taking behavior in non-human subjects. Studies by Piazza and colleagues (6) indicate that a variety of stressors (e.g. tail pinch, social competition) enhance the initiation of intravenous (IV) self-administration of low doses of d-amphetamine in male rats. These findings were recently extended to the initiation (7,8) and maintenance (9,10) of cocaine self-administration (see 11 for a review). Several studies also demonstrate that certain stressors increase alcohol consumption in laboratory rats (see 12 for a review). The present article reviews studies done in laboratory rats, primarily utilizing male subjects, on the effect of stress on opioid self-administration and conditioned place preference and reinstatement of heroin-seeking behavior. Before reviewing these studies, a definition of the stress concept and descriptions of the behavioral methods used in these studies are provided.

The Stress Concept

The concept of stress is defined in terms of its elements: these include the stressors, the stress responses, and factors or processes that mediate the effect of stressors on the organism (1,13,14). Stressors refer to events, perceived or real, that profoundly interfere with the organism's normal steady state. These disruptions comprise the stress response manifested at the physiological (e.g. activation of the sympathetic nervous system), psychological (e.g. anxiety, depression), and behavioral (e.g. performance deficits) levels (14,15). Intervening variables include factors such as constitutional or genetic predisposition and predictability and controllability over the stressors (14–17). These intervening variables influence the relationship between the stressors and the stress responses, leading to large individual differences in response to a given stressor (14).

Several characteristics of stress are relevant to the understanding of the effect of stress on opioid-seeking behavior. First, early theories viewed the stress response as a unitary phenomenon (18). It is now clear, however, that different stressors and even different parameters of exposure to the same stressor lead to different behavioral and physiological responses (13,17,19). In addition, depending on the type of stressor, its parameters (e.g. duration of exposure, intensity), and the stress response being measured, repeated exposure to stress can lead to either tolerance (e.g. 20) or sensitization (e.g. 21,22) to subsequent exposure. Tolerance and sensitization refer to decreases and increases, respectively, in the strength of a response to a stimulus induced by past experiences with the same or related stimuli (23). Finally, prior exposure to stress also modulates the response to drugs. For example, exposure to stress can alter the behavioral effects (e.g. analgesia, locomotor activity) of opioid drugs (24,25).

Behavioral Models

Several laboratory procedures exist to examine factors involved in the behavioral effects of drugs of abuse. This article reviews studies that used three of these behavioral methods: the drug self-administration, the conditioned place preference, and the reinstatement procedure. The basic premise of the drug self-

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Reprint Address: Y. Shaham, Biobehavioral Research Department, Addiction Research Foundation, 33 Russell Street, Toronto, ON M5S 2S1, Canada.

administration method is that psychoactive drugs, like natural reinforcers (e.g. food, water), can control behavior by functioning as positive reinforcers. A stimulus is defined as a positive reinforcer in the operant conditioning paradigm if its presentation increases the likelihood of the responses that produce it (26). In the drug self-administration procedure, the administration of the drug is under the animal's control and, therefore, an objective measure of drug-reinforced behavior can be obtained (27). Opioid agonists are readily self-administered by many species (e.g. rats, mice, monkeys, humans), indicating that they can serve as positive reinforcers (28,29). The self-administration procedure provides a reliable model of drug abuse, and high concordance exists between drugs self-administered by non-human subjects and those abused by humans (28).

The conditioned place preference method is based on the observation that the association of distinctive environmental stimuli with a primary reinforcer (e.g. food, drug) results in an acquired preference for those specific environmental stimuli even in the absence of the primary reinforcer (30). This method is used to measure the reinforcing effects of unconditioned stimuli in a classical conditioning paradigm. Pavlov used the term reinforcement to refer to the strengthening of the association between an unconditioned stimulus and a conditioned stimulus which results when the two events are paired (see 31, p. 380; 32). Many studies have shown that drugs of abuse (including opioid drugs) can establish conditioned place preference in animals or function as reinforcers in a Pavlovian procedure (33). One limitation of the conditioned place preference procedure, however, is that exposure to the drug is not under the control of the subject. On the other hand, an advantage of this procedure is that testing for preference to an environment previously paired with the drug is conducted in a drug-free state. Thus, the results obtained are not confounded by the unconditioned effects (e.g. changes in activity levels) of the drug.

A method used to examine factors involved in relapse to drug-seeking behavior in animals is the reinstatement procedure (34). In this procedure, animals are initially trained to self-administer drugs intravenously. Subsequently, lever presses for drug infusions are extinguished by substituting saline for the drug. After extinction of drug-taking behavior, the ability of a single non-contingent exposure to the training drug (or other drugs or non-drug stimuli) to elicit a period of renewed responding is examined. Studies using this procedure have established that, as in the case of relapse to drug use in humans, reexposure to the previously self-administered drug reliably reinstates drug-taking behavior. Thus, the reinstatement procedure may provide a valid animal model of relapse (35).

Several studies reported that the conditions of social isolation and food deprivation increase opioid self-administration and conditioned place preference (2,36,37). These studies are not reviewed in the present article. Although the findings from these studies are consistent with the findings from the studies reviewed below, it is unclear whether these environmental conditions are comparable to short-term stressors such as restraint, shock, or social defeat. These stressors are operationally different from the conditions of isolation or food deprivation. Exposure to stressors such as restraint, shock, or social defeat consists of the administration of an aversive event to the organism for a limited time period. The putative aversive effect of isolation and food deprivation, in contrast, is the chronic removal of a positive reinforcer (social interaction or food).

REVIEW OF STUDIES

Self-Administration and Conditioned Place Preference

One of the first reports suggesting that stress could increase opioid self-administration was published by Beck and O'Brien (38). Female rats were trained to self-administer IV morphine over a three-week period for 24 hours per day. Each lever press resulted in a brief mild shock to the foreleg (300 Hz for 0.2 or 0.02 second) that was immediately followed by an infusion of morphine (1.0–2.4 mg/kg/infusion). When the shock duration was 0.2 second, but not 0.02 second, all rats increased their response rate until they self-administered lethal doses of the drug. The results of this study, however, are somewhat difficult to interpret because morphine self-administration in the absence of footshock was not measured. Also, the effect of footshock on non-specific behavioral activation (e.g. lever pressing on an inactive lever) was not assessed. Exposure to certain regimens of footshock is known to cause unconditioned behavioral activation (25). Dib and Duclaux (39) trained rats to self-administer morphine intracerebroventricularly (0.5 μg/μl) for one hour per day in operant chambers. During each session, the rats were exposed to 15 minutes of intermittent footshock. The rats increased their lever pressing for morphine during the footshock period compared with the no-shock periods. Footshock did not increase lever pressing when saline was substituted for the drug or when the infusion pump was disconnected.

Several studies have examined the effect of stress on oral opioid self-administration in male rats. In one study (40), the effect of 15 minutes per day of restraint on preference for opioid solutions was examined using a procedure modified from Stolerman and Kumar (41). Animals were given access to morphine or fentanyl solution for four days (forced-consumption sessions) followed by a single choice day of access to the opioid solution and a separate water bottle (a choice-test session). This five-day cycle was repeated five times for seven hours per day in home cages. Restraint was administered for 15 minutes just prior to the period of drug availability. Rats exposed to restraint consumed more morphine or fentanyl during choice tests for the drug versus water than animals not exposed to stress. Exposure to restraint had no effect on opioid consumption during the forced-consumption days and did not alter the preference for an equally bitter quinine solution. In a follow-up study (42), the role of temporal factors in the effect of restraint stress on oral consumption of morphine and fentanyl was examined using the oral self-administration procedure described above (see legend of Figure 1 for the details of the experimental procedure). Results suggest that restraint increases preference for opioid solutions only when it is either paired or partially paired with drug availability, but not when the stressor is explicitly unpaired with the drug sessions.

In order to generalize the results obtained with oral opioid consumption in the home cage to an oral operant self-administration procedure, we trained male rats for approximately one month to lever press for oral fentanyl (50 or 75 μg/ml) under conditions of partial water deprivation (43). Mild intermittent footshock (0.8 mA) was administered for 10 minutes prior to the drug self-administration sessions (30 minutes per day). Testing for oral fentanyl self-administration in the presence or absence of footshock stress was conducted when food and water were continuously available in the home cage for 23 hours per day. Exposure to footshock increased lever presses for oral fen-

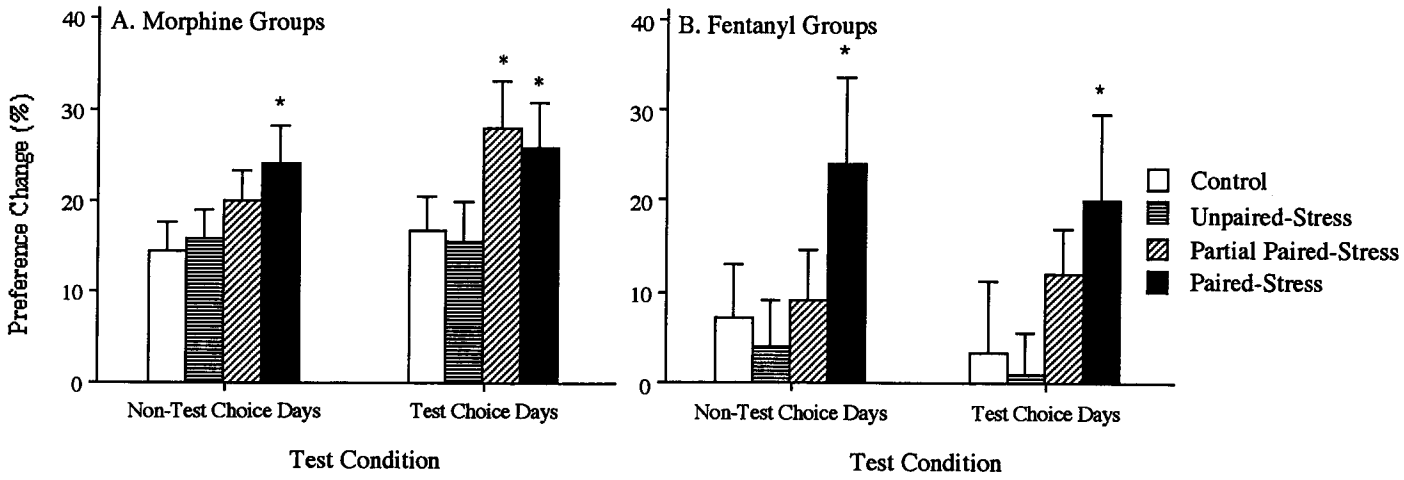

FIGURE 1: Percent of (A) morphine (0.5 mg/ml) and (B) fentanyl (0.25 μg/ml) preference change from the baseline during Test Choice Days (mean of 5 choice days, the drug versus water, conducted every 10 days over a 50-day period) and Non-Test Choice Days (mean of 5 choice days). During Test Choice Days, the animals in the stress groups (i.e. the Paired-Stress, Partial-Paired-Stress, and Unpaired-Stress groups) were exposed to 15 minutes restraint stress just prior to the 6 hours per day oral drug self-administration periods. During Non-Test Choice Days, the Paired-Stress groups were exposed to restraint prior to the drug self-administration period and the Partial-Paired-Stress and Unpaired-Stress groups were exposed to restraint after the drug self-administration period. In the days between the choice days, only the opioid solution was made available to the animals. During these days, animals in the Paired-Stress condition were exposed to 15 minutes of restraint just prior to the 6 hours per day of opioid availability period. Animals in the Unpaired-Stress condition were exposed to restraint one to three hours after the drug sessions. Animals in the Partial-Paired-Stress condition were exposed to restraint within two hours prior to the drug session on half of the days and within three hours after the drug session on the rest of the days. Control groups were not exposed to stress. Compared with the no-stress control condition, increased opioid preference was observed in the Partial-Paired-Stress and Paired-Stress groups, but not in the Unpaired-Stress groups. *–Significant differences from the Control and Unpaired-Stress Conditions. (Data redrawn from Figure 2 in reference 42).

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tanyl self-administration compared with the no-stress condition. The footshock, compared with a no-stress condition, did not alter rates of responding for an inactive (dummy) lever, and it had no effect on rates of responding when the fentanyl solution was replaced with either water or a mildly equally bitter quinine solution.

Together, it appears that under certain conditions footshock or restraint stressors increase opioid self-administration. It also appears that the effects of stress on opioid self-administration are not due to stress-induced changes in fluid consumption, sensitivity to taste, or non-specific behavioral activation. One important issue that remains unclear, however, is whether the results of these studies indicate that stressors alter the positive reinforcing effects of opioid drugs. The increase in rates of responding when footshock is administered during the morphine self-administration sessions (38,39) may occur because the rats learn to increase their morphine consumption in order to decrease the pain induced by the footshock. Also, changes in oral opioid self-administration may be due to stress-induced decreases in the initial aversive effects of exposure to bitter opioid solutions. In addition, the effects of stress were examined on either consummatory behaviors (drinking opioid solutions) or low-response requirements to obtain the drugs (i.e. low-rate fixed-ratio schedules). Under these conditions, it is not possible to determine whether increased opioid self-administration serves to compensate for a decrease in the reinforcing effects of opioid drugs by stress or whether stress actually enhances the reinforcing effects of the drugs directly. This issue was explored in a subsequent study that utilized a progressive ratio schedule of IV heroin self-administration (44).

In the progressive-ratio schedule, the fixed-ratio requirements for obtaining a given reinforcer (i.e. the response requirement) are progressively increased within a session in order to determine the maximum effort that the subject will exhibit. The highest response requirement emitted by the subject before a specified period of no-responding occurs is defined as the final ratio or the breakpoint value (45). In the context of drug self-administration, the final ratio achieved on a progressive-ratio schedule for a drug infusion is thought to reflect the reinforcing efficacy of the drug (see 35,46). In our study, male rats were trained under a fixed-ratio 1 and fixed-ratio 2 schedule of reinforcement to lever press for IV heroin (100 μg/kg per infusion). Animals in the stress condition were exposed to ten minutes of intermittent footshock (0.5 mA) before each of four daily self-administration sessions. Animals in the control group were not exposed to footshock. Following acquisition of the heroin-reinforced behavior, the animals were placed on a progressive-ratio schedule of reinforcement and were tested under a decreasing series of doses. Animals exposed to footshock before each drug session worked for higher final ratios on the progressive-ratio schedule than animals not exposed to stress for heroin doses between 12.5 and 100 μg/kg per infusion, but not for doses below 12.5 μg/kg per infusion (44). These data suggest that footshock increases the reinforcing efficacy of her-

oin (i.e. augments the ability of the drug to sustain drug-reinforced behavior) at the higher dose range.

Together, it appears that footshock or restraint stressors increase opioid self-administration when the stressors are paired or partially paired with the onset of the drug session or when the stressors are administered during the drug self-administration session. It also appears that at a certain dose range stress may increase IV heroin self-administration by enhancing the reinforcing efficacy of the drug.

The effect of stressors on conditioned place preference for morphine has been examined in several studies. One study examined the effect of noise (95 dB) stress on conditioned place preference to morphine (1.5 mg/kg, IP) in male rats (47). The noise was administered while the animals were confined to the drug-paired environment during training. The authors argued that exposure to noise potentiates morphine-induced conditioned place preference. However, the significance of this set of data is not clear. The authors used an unbalanced place preference procedure (see 48) in which the animals had a strong initial preference to the black side (about 28–29 minutes out of the 30 minutes of the baseline sessions), whereas morphine was administered in the white compartment. The effect of noise was to decrease time spent on the black side by about two minutes compared with one minute in the condition of morphine alone. That is, regardless of the experimental condition, a large place aversion was observed to the drug-paired side. The effect of restraint stress on morphine conditioned place preference in male rats was examined in another study by utilizing an apparatus that consisted of a large cage with a small restraint cage inside it (49). The main dependent variable was the number of entries into the restraint (small) cage following sessions in which animals were injected with morphine (0.67 or 2.0 mg/kg, SC) and immediately put into the restraint cage for two hours. Morphine-restraint pairing did not change the number of entries into the restraint cage over time. It is not entirely clear, however, what can be concluded from this study. The authors concluded that exposure to restraint blocked the ability of morphine to produce conditioned place preference. However, an alternative explanation is that morphine prevented place aversion to the restraint cage.

Papp et al. (50) examined the effect of exposure to chronic, long-term, unpredictable, and uncontrollable stress on conditioned place preference to morphine in male rats. This study utilized an unbalanced place-preference procedure in which the rats showed initial preference to the black compartment over the white compartment. Animals in the stress condition were exposed to a variety of chronic unpredictable mild stressors, each applied for a period of 0.5–20 hours (e.g. overnight illumination, intermittent white noise, food and water deprivation, soiled cages, tilted cages, changes in the housing conditions) for five weeks. Subsequently, rats were trained for conditioned place preference to morphine (0.7 mg/kg, IP). Results indicate that irrespective of whether morphine was administered in the initially preferred (black) or the non-preferred (white) side, animals not exposed to stress showed an increase in preference for the drug-associated side. This effect was blocked in animals previously exposed to chronic stress. Thus, it appears that chronic exposure to unpredictable, uncontrollable stress attenuates the reinforcing effects of morphine as measured by a conditioned place preference procedure.

It is not entirely clear what can be concluded from the studies utilizing the conditioned place preference procedure because very different stressors and different doses of morphine were used in these studies. The finding that a chronic mild stress blocks conditioned place preference to morphine (50) appears to be inconsistent with the observation that footshock stress increases IV heroin self-administration under a progressive ratio schedule (44). Possible reasons for these discrepant results are discussed below (see Discussion section).

Reinstatement

In recent years, we have been using a reinstatement procedure in rats to determine the effect of stress on relapse to heroin-seeking in the drug-free state. In the first study (51), the effect of footshock on reinstatement of heroin-seeking was compared to the effects of a priming injection of heroin and a state of acute opioid withdrawal. Male and female rats were trained to self-administer heroin over a two-week period (four three-hour sessions per day; 50 μg/kg/infusion). Subsequently, 16 to 28 (4–7 days) extinction sessions were given, during which lever presses resulted in saline infusions. Animals were then given tests for reinstatement of heroin-seeking behavior following an IV infusion of saline, infusion of heroin (50 μg/kg), exposure to ten minutes of intermittent footshock, and acute precipitated withdrawal [induced by injecting morphine (10 mg/kg, SC) 45 minutes prior to testing, followed by an injection of naltrexone (5 mg/kg, SC) 5 minutes prior to the start of the test session]. Neither saline nor heroin was available during tests for reinstatement. Brief exposure to footshock stress and priming injections of heroin reinstated heroin-seeking behavior (as indicated by renewed responding on the lever that previously delivered heroin) following a period of extinction. By contrast, the aversive state of precipitated withdrawal had no effect on reinstatement of heroin-seeking. Further, both footshock and heroin prime retained their ability to reinstate drug-seeking behavior following a prolonged drug-free period of four to six weeks.

In a follow-up study, we compared the effects on reinstatement of heroin-seeking of three doses of heroin prime to three durations of intermittent footshock (52). Male rats were trained to self-administer heroin (100 μg/kg/infusion, four three-hour sessions/day for eight to eleven days). Extinction sessions were given for five to seven days during which saline was substituted for heroin. Subsequently, reinstatement of heroin-seeking was studied following exposure to different durations of intermittent footshock (10–60 minutes) and different priming doses of heroin (0.125–0.5 mg/kg, SC). Surprisingly, footshock was more effective than the heroin prime in reinstating heroin-seeking (see Figure 2). Neither footshock nor heroin prime significantly increased lever presses on an inactive dummy lever, indicating that increased rates of responding on the lever that previously delivered heroin is not due to non-specific behavioral activation.

Using the same training conditions, we also assessed the role of opioid and dopamine receptors in reinstatement induced by exposure to intermittent footshock (ten minutes) and heroin prime (0.25 mg/kg, SC) (53). Previous studies indicate that opioid and dopamine receptors in the mesolimbic dopamine system are involved in the priming effects of heroin (54,55). During tests for reinstatement, different groups of male rats were pretreated with the opioid antagonist, naltrexone (1 or 10 mg/kg, SC); the non-selective dopamine antagonist (DA), flupenthixol decanoate (3 or 6 mg/kg, IM); the D1-like antagonist, SCH 23390 (0.05 or 0.1 mg/kg, IP); and the D2-like antagonist, raclopride (0.25 or 0.5 mg/kg, IP). The effect on reinstatement

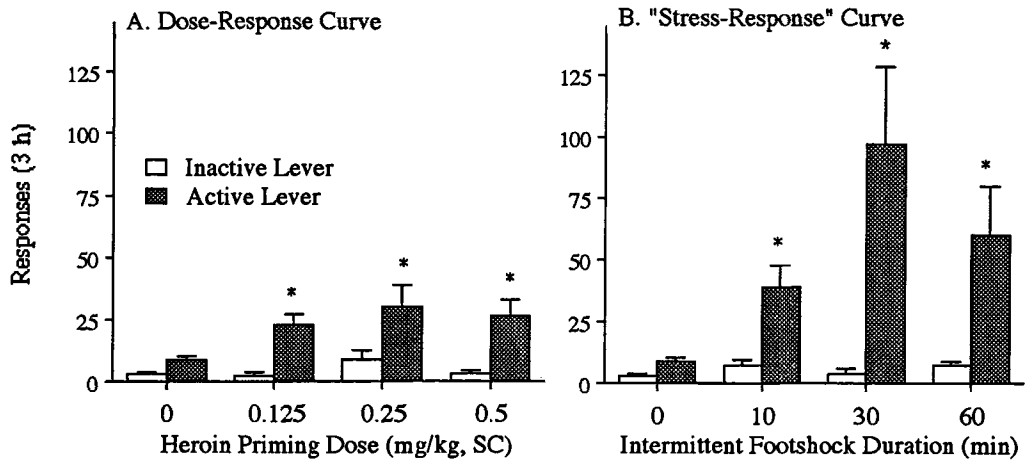

FIGURE 2: Mean (±SEM) number of presses on the previously active and inactive levers in the three hours following a non-contingent SC saline injection, priming injections of heroin (0.125–0.5 mg/kg, SC), and exposure to intermittent footshock stress (10–60 minutes). Each subject was tested with one dose of heroin prime and one duration of footshock following five to seven days of extinction of the heroin-reinforced behavior. Lever presses resulted in saline infusions during the tests for reinstatement. *–Different from the baseline condition (0 minutes of footshock or the 0 dose of heroin prime), $p < 0.05$. (From reference 52).

of the heroin prime was blocked by naltrexone, flupenthixol, raclopride, and the highest dose of SCH 23390, whereas only the non-selective dopamine receptor antagonist, flupenthixol, attenuated footshock-induced reinstatement. These results indicate that the reinstating effects of a footshock and heroin prime can be differentiated pharmacologically.

In a recent study (56), we further examined the effect of footshock on reinstatement of heroin-seeking under conditions that to some degree mimic the conditions of opioid agonist substitution therapy in humans. Male rats were trained to self-administer heroin (100 μg/kg/infusion, IV). Rats were then implanted with Alzet osmotic minipumps that delivered heroin (3 mg/kg/day) at a constant level. Subsequently, the drug-reinforced behavior was extinguished for about one week. A complete description of the results from this study, which primarily assessed the role of opioid withdrawal and reductions in mesolimbic dopamine levels in reinstatement of heroin-seeking, is beyond the scope of this review. But pertinent to the present paper is the observation that the presence of a maintenance dose of heroin during extinction and testing attenuated reinstatement induced by heroin prime (0.25 mg/kg) but did not alter the reinstatement effect of intermittent footshock. This finding provides further support to the notion that footshock- and heroin-induced reinstatements are mediated by different neurochemical events.

Taken together, studies using the reinstatement procedure indicate that stressors may be important stimuli for relapse to heroin-seeking behavior. It also appears that the neurochemical events underlying footshock stress-induced reinstatement are not identical to those that mediate reinstatement after acute reexposure to heroin.

DISCUSSION

In the sections below, factors that appear to be important for the understanding of the effect of stress on opioid-seeking behavior are discussed. These include the temporal relationship between exposure to stress and drug availability and the parameters of stress. In addition, the relevance of the results of the studies reviewed to the understanding of the neurobiology of relapse to opioid-seeking behavior, future research directions, and clinical implications are discussed.

Temporal Factors

The temporal relationship between exposure to stress and drug availability appears to contribute to stress-induced changes in drug-taking behavior. In all of the studies in which stress altered opioid self-administration, the stressor was administered during (38,39) (see also 57) or prior to the drug self-administration sessions (40,42–44). In contrast, when restraint was explicitly unpaired with opioid availability, the stressor did not alter drug self-administration (42) (see Figure 1). Interestingly, a similar effect was observed in a study that examined the role of temporal factors in the effect of restraint stress on sensitization to morphine-induced locomotor activity (58). Repeated intermittent administration of morphine results in increased locomotor activity (sensitization) (59). This behavioral activation and its sensitization are thought to be related to the positive reinforcing effects of opioid drugs (60). In our study, restraint enhanced the sensitization to the locomotor activating effects of morphine only when it was repeatedly paired with the morphine injections. In contrast, when restraint was explicitly unpaired with the drug injections, it had no effect on sensitization to the behavioral activating effects of morphine.

Thus, it appears that the temporal relationship between stress and drug is important for stress-induced changes in the behavioral effects of opioid drugs. The reasons for this temporal effect, however, are not clear. One possibility is that stressors act like conditioned stimuli which reliably predict drug effects. Stimuli repeatedly paired with the effects of drugs have been shown to elicit conditioned responses that, in turn, can alter the unconditioned effects of the pharmacological stimuli (61,62). Stressors may also act as discriminative stimuli which set the occasion under which drug-seeking behavior would lead to drug reinforcement. Studies with humans report that some relapsed addicts claim that stress and negative emotional states often precede their return to drug use or the onset of opioid withdrawal symptoms (63,64). A common interpretation of this stress–relapse relationship is that stressors might serve as con-

ditioned cues that elicit drug craving or drug-like withdrawal symptoms as a consequence of a history of using drugs under conditions of stress (64,65).

However, analysis of stressors as conditioned stimuli is difficult because unlike conventional conditioned stimuli (e.g. lights, tones, specific environments), stressors are not neutral stimuli; they can act as unconditioned stimuli in their own right. Therefore, exposure to stressors that are paired with the drug may alter opioid effects due to the interaction between the unconditioned physiological and behavioral effects of the stressor and some of the actions of the drug, rather than due to a learned association between these events. In fact, it appears that a learned association between stress and drug is not a necessary condition for stress-induced changes in opioid-seeking behavior. In the studies on stress-induced reinstatement of heroin-seeking, footshock was acutely administered for the first time during the testing phase in the absence of the drug. Nevertheless, the stressor reliably reinstated drug-seeking (51–53,56). Further chronic mild stress altered morphine-induced conditioned place preference despite the fact that the stressor was not administered during the training and the testing phases (50).

Taken together, exposure to stress in close temporal contiguity to the drug, as well as prior exposure to stress, can alter the behavioral effects of opioid drugs. It also appears, based on our recent studies on reinstatement of heroin-seeking, that the *temporal contiguity* between stress and drug-seeking behavior rather than the *learned association* between the two events is the critical factor for the effects of paired-stress on drug-seeking.

Parameters of Stressors

An examination of the stressors used in the studies in which it was found that stress alters drug self-administration (38–40,42–44) reveals that they share several common features. The stressors were relatively short in duration, they were administered in close temporal contiguity to the drug, they were administered repeatedly and intermittently, and they appeared to be mild in their intensity. For example, the intensity and duration of footshock in these studies were in general lower than the intensity and duration of the stressor in studies examining behavioral and neurochemical correlates of footshock stress (e.g. 20).

The observation that mild intermittent footshock stressor increases the final ratio for heroin on a progressive-ratio schedule (44) is in direct contrast to the results of Papp et al. (50). These authors reported that chronic stress exposure over several weeks blocks subsequent conditioned place preference to morphine. Several possible reasons exist for these seemingly discrepant results, including the behavioral procedures used, the type of opioid drug, and the route of drug administration. However, it is also possible that the discrepant results between our studies and the Papp et al. study occurred because the type of stressors and their parameters influenced the relationship between stressors and drug-seeking behavior (see below).

Interestingly, a somewhat parallel set of findings, suggesting that different stressors can either enhance or reduce the behavioral effects of positive reinforcers, comes from studies on brain stimulation reward. In the brain stimulation reward procedure, rats are trained to self-administer electrical current to a discrete brain area (66). Short-term restraint (67) or tail pinch (68), which are regarded as mild stressors, increase rates of responding for brain stimulation in male rats. In contrast, long-term chronic unpredictable uncontrollable stress (see 50) for several weeks (69) and acute, severe shock stress (long durations of exposure to shock for up to 18 seconds per minute for 70 minutes) (70) decrease rates of responding and increase the frequency threshold for brain stimulation (see 71 for a review). It should be noted, however, that these seemingly discrepant results in the effects of stressors on brain stimulation should be interpreted with caution. No data are available on the effect of mild stressors on brain stimulation threshold, a more accurate measure of the reinforcing effects of brain stimulation than rate measures (see 72).

Taken together, it is suggested that the duration and the severity of stressors are critical factors in determining whether exposure to stress will enhance or decrease the reinforcing effects of opioid drugs or other reinforcers. It is important to note, however, that the latter conclusion is speculative because there exist no studies that have systematically examined the effects of different parameters of stress on drug-seeking behavior.

Neurobiological Perspective

Stressors alter multiple systems in the brain, and multiple brain systems and neurotransmitters are also involved in the effects of opioid drugs. Consequently, many brain systems and neurotransmitters have the potential to contribute to stress-induced changes in opioid-taking behavior. Stressors are known to activate brain systems involved in both opioid reinforcement and dependence. Restraint, footshock, and other stressors activate noradrenaline neurons in the locus coeruleus, the largest noradrenergic cell body region located in the pons, resulting in physiological and psychological stress responses (73,74). Increased firing rates of these same noradrenergic neurons mediate many of the symptoms of opioid withdrawal (75). Exposure to stress also increases dopamine (see 25,76) and endogenous opioid peptides (77,78) release in the mesolimbic dopamine system, a brain system which contributes to the reinforcing effects of opioid drugs (60,79).

Most studies have examined the effect of stress on opioid self-administration when the drug was available during single daily sessions that lasted from 30 minutes to several hours. Under these conditions, exposure to stressors prior to or during the drug sessions may increase opioid consumption because the stressors alter the reinforcing effects of the drug. Alternatively, the stressor may alter opioid consumption because it exacerbates the opioid withdrawal syndrome. This latter possibility probably cannot explain the effect of footshock on IV heroin self-administration in the study in which the drug was available for four sessions per day (44). Further, exposure to footshock and heroin prime reinstate heroin-seeking behavior after prolonged drug-free periods (51–53,56). Thus, a plausible explanation for the effects of stress on heroin-seeking behavior is that stressors activate certain brain systems in common with those activated by heroin (see 51,80,81). However, the results of our recent study (53) on reinstatement of heroin-seeking suggest that this explanation may not be adequate. As mentioned, the priming effects of footshock stress on reinstatement can be differentiated pharmacologically from those of heroin. Agents that prevented heroin-induced reinstatement (naltrexone and selective dopamine receptor antagonists) did not affect reinstatement induced by exposure to footshock stress. Only a mixed dopamine receptor antagonist was effective in suppressing the reinstating effects of heroin prime and footshock. The observation that an opioid antagonist has no effect on footshock-

induced reinstatement indicates that, unlike heroin prime, stress does not have its effect on reinstatement through the activation of opioid receptors. The discrepancy between the effects of the selective and the mixed dopamine antagonists suggests that footshock-induced reinstatement is not mediated primarily by the mesolimbic dopamine system. Behaviors thought to be mediated by this brain system, such as stimulant drugs self-administration and brain stimulation, are attenuated by either D1- or D2-like receptor antagonists, as well as by mixed dopamine antagonists (82).

Taken together, the hypotheses that stressors alter drug-seeking behavior by activating brain systems involved in opioid reinforcement and dependence cannot explain the data from our recent studies on the effect of footshock on reinstatement of heroin-seeking. Contrary to our expectations, it appears that stressors affect drug-seeking by activating brain systems and neurotransmitters (yet to be identified) that are at least partially distinct from those involved in opioid reinforcement and reinstatement. It is also not very likely that stressors reinstate heroin-seeking by mimicking the opioid withdrawal syndrome (see 64). As mentioned, footshock was highly effective in reinstating heroin-seeking in the presence of a maintenance dose of heroin in the body (56).

Future Directions

There are several ways in which studies on the relationship between exposure to stress and opioid-taking behavior might be extended. These include: (a) the effect of stress on the initiation of opioid self-administration (cf. 6); (b) the effect of other stressors (e.g. social defeat) on opioid-taking behavior; (c) the relationship between the parameters of stress (e.g. intensity, duration, predictability, controllability) and stress-induced changes in drug-reinforced behavior; and (d) the effects of antagonist/agonist drugs of neurotransmitters, other than endogenous opioids and dopamine, on reinstatement of heroin-seeking by stressors. Also, in most of the studies reviewed, the effect of stress on opioid self-administration was examined under limited experimental conditions (i.e. few schedules of reinforcement and limited drug doses). Nevertheless, it appears that the dose of the opioid drug and the schedule of reinforcement can be important factors in the relationship between stress and drug-seeking behavior. For example, footshock had no effect on IV heroin self-administration when low response requirements (FR-1, FR-2 schedules of reinforcement) were used (44). However, the stressor increased drug self-administration when higher response requirements (i.e. a progressive-ratio schedule) were introduced. Also, footshock increased rates of responding when the behavior was reinforced by high drug doses but not when it was reinforced by low drug doses. These observations are important because other events (e.g. pharmacological manipulations) that alter drug-reinforced behavior are, under many occasions, dependent on the dose of the self-administered drug (83). In addition, the schedule of reinforcement used to obtain positive reinforcers determines whether pharmacological agents will increase or decrease rates of responding (the rate-dependent effects of drugs) (see 84). Thus, a better understanding of the conditions under which stress alters drug-reinforced behavior may be obtained by examining a broader range of schedules of reinforcement and drug doses.

Clinical Implications

The studies on the effect of stress on reinstatement of heroin-seeking may have some implications for medications development. Novel drugs for the treatment of drug abuse are tested for their ability to attenuate withdrawal symptoms, substitute for the abused drug, or block the reinforcing effects of the abused drug (85). In addition, although not explicitly stated, an underlying assumption is that an agent that attenuates the reinforcing or the withdrawal effects of the drug of abuse is likely to alter in a similar manner the ability of non-drug stimuli to influence drug-seeking behavior. Our data on the effects of dopamine and opioid antagonists on heroin- and footshock-induced reinstatement suggest that current strategies for medication development may be only partially effective in preventing relapse to drug use. That is, it is likely that pharmacological agents that block the reinforcing or the reinstating actions of heroin will not prevent relapse induced by exposure to stressors. Additional support for this possibility comes from a recent study described above in which we utilized a behavioral model that, to some degree, simulates the condition of opioid agonist–substitution therapy in humans (56). As mentioned, substituting for the self-administered heroin by the delivery of a constant maintenance dose of the drug via an osmotic minipump attenuates heroin-induced reinstatement, but has no effect on reinstatement induced by footshock. Thus, to the extent that the reinstatement procedure provides a reliable animal model of relapse to drug use (34,35), it appears that effective strategies for medication development should also assess the effects of putative novel medications on drug-taking behavior induced by exposure to aversive environmental events.

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