Immobilization stress-induced oral opioid self-administration and withdrawal in rats: role of conditioning factors and the effect of stress on “relapse” to opioid drugs

Yavin Shaham

Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, 1455 de Maisonneuve Boulevard, Montreal, Quebec, Canada H3G 1M8

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Abstract. The effect of 15 min/day of immobilization (IM) stress on oral self-administration (SA) of morphine (0.5 mg/ml) or fentanyl (25 µg/ml) and withdrawal was examined in rats. In addition, the role of conditioning factors in these effects was assessed. For each drug, four groups of subjects were exposed for 50 days to IM stress prior to the drug SA period [Paired-Stress (P-S) groups], to IM stress prior to the drug SA period on half of the days and after the drug SA period on the rest of the days [Partial Paired-Stress (PP-S) groups], to IM stress several hours after the drug SA period [Unpaired-Stress (UP-S) groups], or to no IM stress [Control (C) groups]. The P-S and PP-S groups increased their drug SA during choice days in which both the opioid solution and water were available, and tended to manifest a more severe withdrawal syndrome after a naloxone challenge compared with the UP-S and C groups. Reinstatement of the opioid SA under conditions of paired-stress or no stress was further examined after 3 weeks without exposure to either stress or drugs. The paired stress animals had higher levels of drug SA and manifested a more severe withdrawal syndrome than those tested without stress. These results indicate that the learned association between exposure to stress and the drug availability may mediate, in part, the stress-induced enhancement of opioid SA and withdrawal effects.

Key words: Conditioning – Fentanyl – Morphine – Opioids – Oral self-administration – Relapse – Withdrawal

Human studies indicate that stress is positively related to opioid use and relapse (e.g. Whitehead 1974; Shiffman and Wills 1985; Kosten et al. 1986; O’Doherty 1991). However, these studies are correlational and mostly rely on retrospective self-reports of stress. Thus, no firm conclusion concerning a causal link can be drawn and mechanisms underlying the stress-opioid use relationship cannot be established (O’Doherty and Davies 1987). The theoretical framework guiding many of the human studies is the “stress-buffering hypothesis” which argues that opioid abuse or use may serve as a coping mechanism in order to buffer the aversive aspects of exposure to stress (Alexander and Hadaway 1982; Shiffman and Wills 1985). However, despite the widely held belief in the stress-buffering hypothesis, opioids do not systematically attenuate the expression of physiological systems involved in the stress response, such as peripheral catecholamine functions, and under certain conditions (acute drug exposure) may even enhance the response of the adrenocortical pathway (Buckingham and Cooper 1984; Cox 1988). Opioids do not reliably restore animal behaviors suppressed by aversive stimuli (Houser 1978; Barrett 1987). Finally, the available data do not indicate that opioids attenuate negative mood states (e.g. anxiety, depression) associated with stress (see Mirin et al. 1976).

Because of the methodological and ethical considerations of human research, it may be more suitable to examine the mechanisms underlying the stress-opioid interaction using animal models. Exposure to stressors, such as immobilization and electric footshock, known to affect physiological measures of stress (Selye 1956; Kant et al. 1987), increase intracerebroventricular (Dib and Duclaux 1982), intrathecal (Dib 1985), or oral (Shaham et al. 1992) self-administration (SA) of opioids in animals. However, as in the human literature, these studies did not examine the mechanisms underlying the effect of stress on opioid SA. Further, there exist no animal studies that have examined the effect of stress on opioid SA during a “relapse” phase conducted after an opioid SA period followed by a drug-free period.

The purpose of the present experiment, using an oral opioid SA procedure modified from Stolerman and Kumar (1970), was three-fold. The first purpose was to replicate previous findings from our laboratory (Shaham et al. 1992) of the effect of IM stress in increasing oral opioid SA in rats. The second purpose was to examine the effect of IM stress on opioid SA during a “relapse” phase conducted after a prolonged opioid SA period followed by a drug-free period. Third, the present experiment was de-
signed to examine whether learning mechanisms are involved in the IM stress-induced opioid SA and withdrawal. Specifically, based on the finding that conditioning factors are involved in drug tolerance and dependence (see Eikelboom and Stewart 1982; O'Brien et al. 1986; Siegel 1989), it was hypothesized that the learned association of the temporal relationship between exposure to IM stress and the drug availability may mediate, in part, the stress-induced changes in opioid SA and withdrawal. In order to test the learning hypothesis, exposure to 15 min/day of IM stress was paired with, partially paired with, or explicitly not paired with the drug SA period. The latter two temporal arrangements were chosen because they attenuate the acquisition of a given conditioned response (Mackintosh 1983). It was hypothesized that compared with a control condition of no exposure to stress, increased opioid SA and opioid withdrawal would only occur when IM stress is paired or partially paired with the opioid SA period, but not in a condition in which the stressor is explicitly unpaired with the opioid SA period. It was further hypothesized that a faster rate of acquisition of opioid SA would occur in the paired condition compared with the partially paired condition.

Material and methods

Subjects. Sixty-six male Wistar rats (Charles River; 250–300 g at the start of the experiment) were the subjects. Animals were individually housed in polypropylene cages (35.6 cm × 15.2 cm × 20.3 cm) at a temperature of 23°C, relative humidity of 50%, and light-dark cycles of 12 h each (light on 0700–1900). Food (standard rodent chow) was available continuously.

Drugs and solution consumption schedule. Morphine sulfate powder (Mallinckrodt), in concentrations of either 0.25 or 0.5 mg/ml dissolved in tap water, or fentanyl HCl (NIDA), in a concentration of 25 μg/ml dissolved in tap water, were used. Naloxone HCl (Dupont) dissolved in physiological saline was used to precipitate the withdrawal syndrome. All animals had access to either an opioid solution alone or a choice between this solution and water in cycles of 1 day of choice followed by 4 days of no choice [forced consumption (FC) days]. The oral opioids or water were made available for 6 h/day in the home cages during the FC and the choice days (between 10 a.m. and 4 p.m.). The opioid solutions or water were not available between 4 p.m. and 10 a.m. The placement of the bottles was counter-balanced daily in the left and right positions of the cages.

Stress manipulation. The stress manipulation consisted of transferring the animals from the colony room to a nearby room in which they were immobilized for 15 min by a finger-like immobilization apparatus (Fisher Scientific, # 01-282-1; 32 × 10 × 8.9 cm) consists of 12 finger-like projections on each side that can be adjusted to animal sizes from 150 to 800 g. Two plastic stoppers on each side of the apparatus keep the animal from escaping. The flexible rib construction secures the animals so that they cannot move, yet expands with minor body movement.

Assessment of physical dependence. Naloxone at a dosage of 1 mg/kg IP was used to precipitate the opioid withdrawal syndrome. Assessment of the withdrawal syndrome lasted 20 min after the naloxone injection and was conducted by two independent observers. The following withdrawal symptoms were counted (e.g. Linseman 1977): diarrhea episodes, teeth chattering, excessive grooming, abnormal posture, wet-dog shaker, piosis, and body weight change 25 min after the naloxone injection.

Procedure. For 6 days before the introduction of the drugs, baseline water consumption for 6 h/day and body weight were determined. Prior to phase 1 of the experiment (see below), a baseline choice day was conducted between 0.5 mg/ml morphine and water or 25 μg/ml fentanyl and water. For each drug, animals were divided into four experimental groups (see below) matched for their initial drug preference. In the morphine groups, the next choice day between 0.5 mg/ml morphine and water was conducted after 4 days of access to a diluted morphine solution of 0.25 mg/ml. The experiment was conducted in three phases.

The initial phase (phase 1, days 1–51) included ten FC periods of 4 days each and 10 choice days between the opioids versus water; a stress-free phase (phase 2, days 52–61) including 2 choice days and two FC periods during which the opioids were available in the absence of stress in all groups; and phase 3 (a “relapse” phase, days 81–110) included five FC periods and 5 choice days of exposure to IM stress followed by 1 FC period and 1 choice day in the absence of IM stress. Phase 3 was conducted 3 weeks after the end of phase 2. During the 3-week period, all animals were drug-free and stress-free. In phase 1 of the experiment, for each drug, four experimental groups (n = 8–9) were examined. Paired-Stress (P-S) animals were exposed to IM stress just prior to the drug SA period during the FC days and choice days (i.e. the drug solution was made available within 5 min after exposure to IM stress). The Unpaired-Stress (UP-S) animals were exposed to IM stress within 1–3 h (between 5 p.m. and 7 p.m.) after the end of the drug SA period during the FC days and during odd choice days [Choice Days 1, 3, 5, 7 and 9; Non-Test Choice Days (see below)]. The IM stress administration in this group during even choice days [Choice Days 2, 4, 6, 8, 10; Test Choice Days (see below)] was temporally identical to the P-S group (i.e. just prior to the drug SA period). The Partial Paired-Stress (PP-S) animals were exposed to IM stress either before or after the drug SA. Specifically, during the FC days, the IM stress was administered at pre-determined random times within a window of 0–2 h prior to (between 8 a.m. and 10 a.m.) or 0–3 h after the drug SA period (between 4 p.m. and 7 p.m.) so that on half of the days IM stress was administered prior to the drug SA and on the other half of the days IM stress was administered after the drug SA period. The IM stress administration in the PP-S groups during the choice days was identical to the UP-S groups. Control (C) animals were...