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Naloxone, not proglumide or MK-801, alters effects of morphine preexposure on morphine-induced taste aversions

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Abstract

Both cholecystokinin (CCK) antagonists and *N*-methyl-D-aspartate (NMDA) antagonists block or reduce the development of morphine tolerance in several analgesic assays. The present experiments were performed to assess the ability of the CCK antagonist proglumide and the NMDA antagonist MK-801 to affect tolerance to the aversive properties of morphine as indexed by conditioned taste aversion (CTA) learning. Specifically, male Sprague–Dawley rats were exposed to either vehicle or morphine (5 mg/kg) in combination with either proglumide (5 mg/kg; Experiment 1), MK-801 (0.1 mg/kg; Experiment 2) or naloxone (1, 3.2 mg/kg; Experiment 3). Saccharin was then presented and was followed by an injection of either vehicle or morphine (10 mg/kg). Animals preexposed to and conditioned with morphine acquired an attenuated morphine-induced aversion to saccharin. While neither proglumide nor MK-801 had an effect on this attenuation, naloxone blocked the effects of morphine preexposure, suggesting that neither CCK nor NMDA may be involved in the aversive effects of morphine (or their modulation by drug exposure). That the attenuating effects of morphine preexposure on a morphine-induced CTA can be blocked suggests that the weakening of the aversive effects of morphine with chronic use can be prevented, an effect that may have implications for overall drug acceptability.

Keywords: Taste aversion; UCS preexposure; Tolerance; Morphine; Proglumide; MK-801; Naloxone; NMDA; CCK

1. Introduction

Although animals readily acquire an aversion to tastes paired with morphine (see Hutchinson et al., 2000; Mucha and Herz, 1985; Riley et al., 1978; Switzman et al., 1981), these aversions are significantly attenuated if animals have a history of morphine prior to conditioning (Dacanay and Riley, 1982; Domjan and Siegel, 1983; Riley et al., 1984; Simpson and Riley, 2005; Stewart and Eikelboom, 1978), a suggestive effect of tolerance to its aversive effects (see Cappell and LeBlanc, 1977; Riley et al., 1976; though see de Brugada et al., 2004, 2005). Although the effects of drug preexposure are well documented in taste aversion learning in general, and with morphine more specifically (for a review, see Randich and LoLordo, 1979; Riley and Simpson, 2001), it is not known to what extent (if any) these effects can be modulated either behaviorally or pharmacologically. An understanding of what factors can modulate the attenuating effects of drug history on taste aversion learning may be important given that a drug's abuse potential is a function of the balance of its aversive and rewarding effects. Any manipulation that impacts either of these affective properties is likely to affect the vulnerability to the use and abuse of that compound.

Interestingly, tolerance to the analgesic effects of morphine (Dourish et al., 1990; Zhou et al., 1992) has been reported to be blocked by a variety of compounds. For example, both cholecystokinin (CCK) antagonists, such as proglumide, and the non-competitive *N*-methyl-D-aspartate (NMDA) antagonist MK-801 have been shown to block or reduce the development of morphine tolerance in several assessments of analgesia,

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including the hot-plate and tail-flick tests (Bhargava and Matwyshyn, 1993; Dourish et al., 1988, 1990; Hoffmann and Wiesenfeld-Hallin, 1994; Kellstein and Mayer, 1991; Panerai et al., 1987; Singh et al., 1996; Tang et al., 1984; Tortorici et al., 2003; Trujillo and Akil, 1991, 1994; Watkins et al., 1984; Xu et al., 1992). Given the effects of CCK and NMDA antagonists on the development of tolerance to morphine's analgesic effects, it is possible that proglumide and MK-801 could modulate the development of tolerance to the aversive effects of morphine. To explore this possibility, the current studies were performed to investigate the effects of the non-selective CCK antagonist proglumide (Experiment 1), the non-competitive NMDA antagonist MK-801 (Experiment 2) and the non-selective opioid antagonist naloxone (Experiment 3) on the morphine preexposure effect in taste aversion learning. Specifically, animals were exposed to morphine in combination with either proglumide, MK-801 or naloxone prior to taste aversion conditioning during which a novel saccharin solution was paired with morphine on four separate conditioning trials. Saccharin consumption was assessed on each of these days, as well as on a final aversion test.

2. General method

2.1. Subjects

Subjects were 230 experimentally-naïve male Sprague–Dawley rats, approximately 60–100 days in age and approximately 275–500 g in weight at the beginning of the experiments. Animals were housed individually in stainless-steel, wire-mesh cages and maintained on a 12-h light/12-h dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiments. Standard rat chow and water (except where noted) were available ad libitum. Animals were housed for approximately 2 weeks prior to the commencement of each experiment for habituation to their new environment. Procedures recommended by the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Drugs and solutions

Morphine sulfate, naloxone hydrochloride (both generously provided by the National Institute on Drug Abuse) and MK-801 were dissolved in distilled water. Proglumide (obtained from Panos Therapeutics) was suspended in a solution of 1.2% DMSO in 7.0 pH buffer solution. All drugs were administered by intraperitoneal (i.p.) injection and prepared in the following concentrations: morphine (5 mg/ml), MK-801 (10 mg/ml), naloxone (1 mg/ml), proglumide (5 mg/ml). Saccharin (0.1% sodium saccharin, Sigma Chemical Company) was prepared as a 1 g/l solution in tap water.

2.3. Procedure

Phase 1: Water habituation. Following 23-h water deprivation, animals were given 20-min access to water. This procedure was repeated each day until all subjects drank within 2 s of water presentation.

Phase 2: Preexposure. At the outset of this phase, animals were assigned to a drug preexposure group based on the average amount of water consumed over the last 3 days of water habituation. On Day 1 of this phase, animals received their regular 20-min access to water. Five hours later, all subjects were injected with one of the aforementioned compounds (proglumide, MK-801, naloxone or vehicle), and subjects then received injections of either morphine or vehicle. These drug combinations were administered every other day for a total of five preexposure days. Animals received 20-min access to water on the recovery day between each preexposure session, as well as on the day following the last drug preexposure. No injections were administered following water access on these days.

Phase 3: Conditioning. On the second day after the last drug preexposure session in Phase 2, all animals received 20-min access to a novel saccharin solution. Immediately following access to saccharin, each preexposure group was divided in half such that saccharin consumption was comparable between groups. Each animal then received an i.p. injection of either morphine (10 mg/kg) or the distilled water vehicle. On the following three water-recovery days, all animals received 20-min access to water. No injections followed water access on those days. This alternating procedure of conditioning followed by three water-recovery days was repeated for four complete cycles.

Phase 4: Final aversion test. On the day after the final water-recovery session of Phase 3, animals received 20-min access to saccharin in a final test of the aversion to saccharin. No injections followed saccharin access on this test day.

2.4. Group names

Group names are such that the first set of letters refers to the first (proglumide (P), MK-801 (Mk), naloxone (n, 1 mg/kg; N, 3.2 mg/kg), vehicle (V)) and second (morphine (M), vehicle (V)) drugs administered during preexposure. One group of animals received an injection of proglumide followed immediately by morphine (PiM). The last letter refers to animals administered morphine (M) or vehicle (V) during conditioning.

2.5. Statistical analysis

For each experiment, repeated measures analyses of variance (ANOVAs) with one between-group factor (Group) and one within-group factor (Preexposure Day) were performed on mean water consumption during preexposure. A Group × Trial repeated measures ANOVA was performed to assess differences in saccharin consumption among the control groups (i.e., all animals receiving vehicle during conditioning) within each experiment. There were no significant differences among any of these groups. Consequently, the control groups within each experiment were combined for all further analyses. For each experiment, a repeated measures ANOVA with one between-group factor (Group) and one within-group factor (Trial) was performed to compare saccharin consumption during conditioning. Post-hoc analyses were conducted using