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Research report

Trial-selective effects of U50,488H, a κ-opioid receptor agonist, on consummatory successive negative contrast

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ABSTRACT

A series of experiments studied the effects of the κ-opioid receptor agonist U50,488H on consummatory successive negative contrast (cSNC) in rats. In cSNC, previous experience with a 32% sucrose solution leads to greater rejection of 4% sucrose than exclusive experience with 4% sucrose. Experiments 1 and 2 revealed that U50,488H failed to influence cSNC when administered before the first downshifted trial, but either attenuated (1 mg/kg) or enhanced (3 and 10 mg/kg) cSNC when administered before the second downshift trial. Experiment 3 showed that U50,488H administered immediately after the first downshift trial had no effect on cSNC at the 1 mg/kg dose, but tended to increase cSNC at the 3 mg/kg dose. However, Experiment 4 suggested that the apparent enhancement of cSNC after 3 mg/kg U50 administered posttrial 11 may have reflected the development of a conditioned taste aversion. The trial-selective attenuating effect of the low dose may reflect an anxiolytic-like property of U50,488H.

1. Introduction

The opioid system is one component of a set of mechanisms mediating the response to surprising reward loss, as studied in the consummatory successive negative contrast (cSNC) situation [41]. In the cSNC situation, the consummatory performance of rats given free access to 32% sucrose solution during short daily trials is compared after a downshift to 4% sucrose with that of an unshifted group always exposed to 4% sucrose. Downshifted rats exhibit a transient suppression of consummatory behavior relative to unshifted controls, followed by the recovery of normal levels of consummatory behavior after 2–4 daily trials of access to the downgraded solution [15]. Experiments show that the nonselective opioid receptor agonist morphine (4–8 mg/kg, i.p.) administered before either the first or second downshift trial (usually trials 11 and 12, respectively) attenuates cSNC on both trials, thus accelerating recovery [47]. Complementary to these results, the nonselective opioid receptor antagonist naloxone (2 mg/kg, i.p.) administered before trials 11 and 12 enhances cSNC on both trials, thus interfering with recovery from reward loss [44]. Both morphine and naloxone are considered nonselective opioids as far as their receptor-binding properties. However, greater affinity for the μ receptor in both drugs has been reported [29]. If correct, the μ-opioid receptor subsystem may not play a selective role on the first versus second postshift trials in cSNC.

Additional evidence suggests that the δ-opioid receptor subsystem selectively mediates the initial response to reward loss, but not the recovery that follows. For example, the selective δ-opioid receptor agonist D-Ala2-,N-MePhe4,Phe4,Gly-ol (DPDPE, 24 μg/kg, i.p.) attenuates the initial impact of reward downshift on trial 11, but fails to affect recovery from reward downshift on trial 12 [54]. Moreover, the selective δ-opioid receptor antagonist naltrindole (1 mg/kg, i.p.) administered before trials 11 and 12 enhances cSNC on trial 11, but has no detectable effect on trial 12 [44]. Whereas several drugs are known to attenuate cSNC selectively on trial 12 (e.g., benzodiazepine anxiolytics; [15]), the selective effects of δ opioids on trial 11 provide the first evidence identifying a neurochemical system involved in modulating the initial reaction to surprising reward downshifts. This discovery provided the impetus for exploring the action of other opioid receptor selective peptides.

This paper reports evidence on the effects of pretrial and posttrial administration of the selective κ-opioid receptor agonist U50,488H (heretofore U50) on cSNC. The general goal is to determine whether activating the κ-opioid receptor subsystem would affect cSNC and, in the affirmative case, whether the effect is selective for trial 11 vs. trial 12 performance. Virtually nothing is known about the role of the κ-opioid receptor subsystem in situations involving reward loss. Following a well-known parallel between the mechanisms subserving pain-fear and frustration [19,39,41], it may be profitable to look for potentially relevant evidence

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in experiments involving fear conditioning. For example, freezing responses in Pavlovian fear conditioning increase following administration of the μ antagonist CTOP, but decrease following administration of the κ antagonist nor-binaltorphimine [14]. Administration of cyprenorphine and naltrindole (δ-opioid receptor antagonists) revealed no effects compared to saline controls. Furthermore, Osaki et al. [39] tested the effects of naloxonazine (μ antagonist) and nor-binaltorphimine (κ antagonist) administered into the periaqueductal gray and inferior colliculus on fear-like behaviors (running and jumping) after electrical stimulation of the central nucleus of the inferior colliculus. Naloxonazine increased and nor-binaltorphimine decreased the defensive threshold, suggesting that the κ-opioid receptor subsystem may regulate μ-mediated behaviors. These results suggest, first, that the μ- and κ-opioid receptor subsystems can oppose each other and, second, that these different opioid subsystems can have differential effects on fear conditioning. Together with the differential effects of DPDPE on cSNC reviewed previously, all three major opioid receptor subtypes are implicated in different roles in cSNC.

Four experiments are reported in this article. Experiment 1 addressed the effects of U50 when administered before postshift trials 11 and 12. Experiment 2 evaluated the effects of U50 administered only before postshift trial 12. Experiment 3 looked at the effects of U50 administered after postshift trial 11. Finally, Experiment 4 tested the hypothesis that the posttrial effects observed in the previous experiment were due to the rapid development of a U50-induced conditioned taste aversion. All together, these experiments demonstrate another selective action of an opioid agonist on cSNC, suggesting that under some conditions, the δ- and κ-opioid subsystems modulate cSNC selectively on trials 11 and 12, respectively.

2. Experiment 1

As mentioned previously, various opioid treatments can have opposite effects on behavior. For example, Ilyutchenok and Dubrovina [23] demonstrated that reacquisition of one-trial passive avoidance was enhanced by ICI 174,864 (δ antagonist) and dynorphin (κ agonist). Similarly, morphine self-administration [16] and morphine-induced locomotion [42] were suppressed by U50 in adult rats. In addition, preadolescent rats showed impaired morphine-induced place preference [8] and increased vocalizations [35] following U50 administration. Vocalizations were suppressed following administration of the κ-opioid receptor antagonist nor-binaltorphimine. Narita et al. [34] reported that the straub tail reaction induced by intracerebroventricular injections of morphine was significantly antagonized by beta-funaltrexamine (μ antagonist), and by U50 (κ agonist). Analogous opposing effects were obtained in some neurophysiological studies. For example, Walker et al. [53] found that activation of the κ-opioid receptor subsystem by U50 suppressed the firing of neurons activated by morphine in the substantia nigra. The fact that κ modulation leads in some cases to opposite effects from those found after μ and δ modulation is consistent with the differential distribution of these opioid receptors in the rat brain [30].

In addition to U50 showing opposite effects to those of μ- and δ-opioid receptor agonists, the dose level can affect behavior differentially. For example, Schnur and Walker [50] observed locomotor hyperactivity after administration of a low dose of U50 (1 mg/kg, i.p.), but locomotor hypoactivity after administration of a high dose of U50 (10 mg/kg, i.p.), relative to saline controls in hamsters. Apart from the potential species differences, this study suggests the possibility that the level of κ activation induced by the administered dose can cause opposite behavioral effects. Experiment 1 had two goals. First, to determine whether opposing effects similar to those described for locomotor activity are observed in the cSNC situation after administration of U50, and second, to determine whether the effects were behaviorally selective for the first vs. second postshift trials. Independent groups of rats received treatment with U50 (0, 1, 3, and 10 mg/kg, i.p.) before trials 11 and 12, while being either downshifted or unshifted in terms of incentive magnitude. Thus, two sets of controls were implemented: a drug control (saline treatment) and a contrast control (unshifted incentive treatment).

2.1. Method

2.1.1. Subjects

The subjects were 64 adult Long-Evans rats, 90–110 days old at the start of the experiment. Thirty-two males and 32 females were used. Both male and female rats are used whenever possible, as done in most previous experiments on cSNC from our lab. Rats were bred in the TCU vivarium from parents purchased at Harlan. Animals were housed under a 12:12 h light:dark cycle (lights on at 07:00 h) and behaviorally tested during the light phase of the cycle. In preparation for the experiment, all rats were deprived of food to an 81–84% of their ad libitum body weight. Water was freely available in the home cage.

2.1.2. Apparatus

Animals were tested in four conditioning boxes constructed of aluminum and Plexiglas, 29.3 cm long, 21.3 cm high, and 26.8 cm wide. The floor was made of steel rods 0.4 cm in diameter and 1.6 cm apart that ran parallel to the feeder wall. A tray filled with corncob bedding was placed below the floor to collect fecal pellets and urine. A sipper tube (1 cm in diameter and flush against the feeder wall when fully inserted) was automatically inserted and retracted to deliver the sucrose solution. This sipper tube was inserted through an elliptical hole in the feeder wall, 1 cm wide, 2 cm high, and 4 cm from the floor. Contact with the sipper tube was recorded automatically by the closing of an electric circuit between the sipper tube and the steel floor.

The conditioning box was enclosed in a sound-attenuating chamber 57.5 cm long, 36.9 cm high, and 39.4 cm wide. This chamber also had a speaker and a fan, which register 80.1 dB (SPL, scale C). The control of the sipper tube and recording of the response were performed by a computer located in an adjacent room.

2.1.3. Procedure

Animals were exposed to the conditioning box for a total of 14 trials, 10 preshift trials and 4 postshift trials. Testing consisted of a 5-min access to the sucrose solution starting from the first contact of the rat with the tube. Each trial started and ended with a variable interval averaging 30 s during which the sipper tube was retracted. These intervals were introduced to remove the handling events that precede and follow a trial from consummatory behavior occurring during the trial. Downshifted animals received access to 32% sucrose on preshift trials 1–10 and then 4% on postshift trials 11–14. Unshifted animals received 4% in both pre- and postshift trials. One trial per day was administered. Sucrose solutions were prepared (w/w) by mixing 4 g (or 32 g) of sucrose per 96 g (or 68 g) of distilled water. Random assignment was used to determine which animals received access to 32% sucrose or to 4% sucrose during the preshift trials. Thereafter, the performance of rats on preshift trials was matched before randomly assigning individual animals to the various groups exposed to downshifted or unshifted conditions. Thirty-two animals received a 32-4 downshift, were matched, and then randomly assigned to four drug conditions ($n = 8$). Group 32/S, 32/1, 32/3, and 32/10 received, respectively, injections of saline, 1, 3, or 10 mg/kg. Thirty-two animals were matched and then randomly assigned to the unshifted 4-4 contrast control condition and randomly assigned to four groups ($n = 8$). Groups 4/S, 4/1, 4/3, and 4/10 received, respectively, injections of saline, 1, 3, or 10 mg/kg. All drugs were administered i.p. 20 min before the start of trials 11 and 12. Saline injections were of equal volume. These doses were based on Schnur and Walker's [50] experiment. *Trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclo-hexyl]-benzeneacetamide (U50,488H) was prepared by mixing the appropriate amount of desiccate with 1 ml of saline. The stock solution was then diluted to the appropriate doses. Doses were prepared 48 h prior to the first postshift trial (trial 11). Isotonic saline solution was used as vehicle. Drugs were purchased from Sigma–Aldrich Chemicals (Saint Louis, MO).

The dependent variable was the cumulative time in contact with the sipper tube (in 0.05-s units), up to a maximum of 5 min. Under the conditions used in the present experiments, this dependent variable (named goal-tracking time) produces less variable data than the more typical licking frequency measure used in other labs. Goal-tracking time has been reported in previous research [44,54], it has yielded significant positive correlations with amount of fluid intake [33], and it has recently replicated within a single experiment the selective effects of chlordiazepoxide on trial 12, but not on trial 11, previously reported in separate experiments [12]. Goal-tracking time yields nonsignificant preshift differences in some experiments, but this is not uncommon with lick frequency data (for one example, see [15], p. 56). Goal-tracking times were subject to conventional analysis of variance. Multiple comparisons were computed using Fisher's LSD post-hoc test. In all the statistical tests, the alpha value was set at the 0.05 level. Due to experimental error, two females in the 4% sucrose condition received fewer than 10 trials of testing; the data from these two animals were excluded.

2.2. Results

Fig. 1 displays the consummatory performance of the eight groups segregated by dose. Overall preshift performance shows a trend toward greater response level in groups receiving access to 32% sucrose than to 4% sucrose. A Contrast (32% vs. 4% sucrose) × Sex × Trial (1–10) analysis indicated the following results. There was a significant triple interaction, $F(9, 540) = 2.03$, $p < 0.04$, but neither the main effect of sex, the sex by trial interaction, or the sex by contrast interaction reached significance, $Fs < 2.26$, $ps > 0.13$. Goal-tracking times were significantly higher for rats drinking 32% sucrose than 4% sucrose, $F(1, 60) = 6.61$, $p < 0.02$, but tended to converged on later trials, as is usually the case, yielding a significant sucrose by trial interaction,