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Long-Term Voluntary Access to Running Wheels Decreases Kappa-Opioid Antinociception

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D'ANCI, K. E., GERSTEIN, A. V. AND KANAREK, R. B. *Long-term voluntary access to running wheels decreases kappa-opioid antinociception.* PHARMACOL BIOCHEM BEHAV **66**(2) 343–346, 2000.—Previous research has demonstrated that voluntary exercise is associated with a reduction in mu-opioid-induced antinociception. To determine if the effects of voluntary exercise on opioid-induced antinociception were limited to drugs that affect the mu opioid receptor or were more general, the analgesic effects of the kappa opioid agonist U50,488H were compared in active and sedentary rats. Eight adult male Long-Evans rats were housed in standard hanging cages and eight in cages with attached running wheels for 20 days prior to antinociceptive testing. Pain thresholds were determined using a tail-flick procedure, and antinociception was expressed as percent maximal possible effect (%MPE). In the first study, U50,488H was administered in a cumulative dosing procedure (5.0, 10.0, 20.0 mg/kg). Tail-flick latencies were measured immediately prior to and 30 min following each injection. In the second study, the time course of U50,488H effects was examined in animals from the first experiment. Tail-flick latencies were measured immediately prior to and 30, 60, and 90 min following 10.0 mg/kg U50,488H. In the first study, U50,488H produced significant antinociception in both groups of rats. However, antinociceptive responses were significantly reduced for rats given access to running wheels relative to inactive rats. In the second study, antinociceptive responses to U50,488H continued for 90 min. Again, antinociceptive responses were lower for rats given access to running wheels relative to inactive rats. These results indicate that long-term voluntary exercise decreases the antinociceptive properties of the kappa agonist U50,488H, as well as the mu agonist morphine. © 2000 Elsevier Science Inc.

Kappa opioids U50,488H Antinociception Analgesia Tail-flick Pain Exercise Running wheels Activity Long-Evans Rats Male

RECENT studies show that voluntary running wheel activity alters behavioral responses to psychoactive drugs (13,16,19). For example, access to running wheels reduces oral intake of opiates (19; Kanarek and Marks-Kaufman, unpublished data) and decreases morphine-induced antinociception (16). Other research demonstrates that aerobic exercise produces elevated plasma and central beta-endorphin levels in both humans and animals (4,5). It is possible, therefore, that these exercise-related increases in endogenous mu-opioid peptide levels influence sensitivity to mu opiate drugs. As we reported previously (16) chronic elevations in endogenous opioid activity may result in cross-tolerance to the effects of exogenously administered opioids, and one indication of this cross-tolerance is a consistent reduction in the antinociceptive properties of morphine in chronically exercised rats relative to inactive controls (16). This proposal is supported by evidence of cross-tolerance between morphine and beta-endorphin (21).

Aravich and colleagues (1) reported that hypothalamic dynorphin-A levels were elevated after relatively short-term (4 days) voluntary access to running wheels. Because dynorphin-A binds to kappa opioid receptors with high affinity (18), we undertook the present study to determine whether kappa opioid antinociception was similarly reduced in rats given access to exercise relative to sedentary rats. To evaluate this hypothesis, the ability of voluntary running wheel activity to alter the antinociceptive properties of the kappa-opioid receptor agonist U50,488H was examined. Baseline nociceptive

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thresholds and nociceptive thresholds following administration of U50,488H were determined in rats housed in running wheels (active) and rats housed in standard cages (inactive). Two studies were conducted; in the first, a cumulative dose response curve was generated for U50,488H in both groups of animals. In the second experiment, time course data were collected at 30, 60, and 90 min following administration of the dose that produced the greatest group differences in the first experiment.

METHOD

Subjects

Sixteen adult male Long-Evans VAF rats (Charles River, Kingston, MI, USA) weighing between 275 and 300 g at the beginning of the experiment were used. Eight rats were housed individually in standard stainless-steel hanging cages and 8 were housed individually in Wahman (Timonium, MD, USA) LC-34 activity wheels with adjoining cages. Wheel turns were measured with a microswitch such that only complete 360° turns were recorded. Animals were housed in a temperature-controlled room (21° ± 2°C) and maintained on a 12:12 h reverse light-dark cycle (lights on: 2000 h). Consistent with our earlier studies examining opioid-induced antinociception (9,12,14–16), all experimental procedures were conducted under red lights during the middle of the dark cycle (1000 to 1600 h).

All rats were given ad libitum access to ground Purina chow (#5001) and tap water. The chow was presented in Wahman LC-306A stainless-steel food cups with lids. The food cups were clipped to the cage floors to prevent spillage. Water was available in glass bottles fitted with drip-proof stainless-steel stoppers. Food and water intakes, body weights, and wheel revolutions were measured every other day. Rats were given 20 days to acclimate to the handling procedures, lighting conditions, and to the running wheels prior to onset of antinociceptive testing. All procedures were approved by the Tufts University animal care and use committee.

Drugs

U50,488H (Research Biochemicals International, Natick, MA, USA) was dissolved in 0.9% saline and administered subcutaneously in a volume of 1.0 mg/kg. In the part of the first study, U50,488H was given according to a cumulative dosing procedure (5.0, 10.0, 20.0 mg/kg), with injections 30-min apart. In the second part of the study, a single injection of 10.0 mg/kg U50,488H was used.

Antinociceptive Testing

Pain thresholds were determined using the radiant-heat tail-flick assay (8) as described extensively elsewhere (3,9,16). Briefly, rats were gently held in a clean cloth by the same experimenter and placed on a tail-flick apparatus (Emdie Instrument Co., Montpelier, VT, USA). Baseline tail-flick latencies were determined prior to administration of U50,488H. Antinociception was measured 30 min after each cumulative dose (5.0, 10.0, 20.0 mg/kg) or 30, 60, and 90 min after injection of 10.0 mg/kg U50,488H.

Statistical Analysis

Prior to statistical analysis, tail-flick latency data were converted to the percent maximal possible effect (%MPE), which was calculated as follows:

$$\%MPE = \frac{(\text{test latency} - \text{baseline})}{(\text{maximal latency} - \text{baseline})} \times 100$$

where the maximal latency was the cutoff time of 10 sec. The data were then analyzed with two-way ANOVAs (running condition × dose) or (running condition × time after injection) with dose or time as a repeated measure. Post hoc comparisons were done with Bonferroni-Dunn *t*-tests to determine specific differences between groups. To identify rats with significantly high or low baseline tail-flick latencies, boxplots were generated (SPSS for Windows, Rel. 7.0.0 1995, SPSS Inc., Chicago, IL, USA) for all baseline tail-flick latencies. Using this method, one animal in the inactive group in the second study was removed from data analysis as a statistical outlier.

RESULTS

Wheel Revolutions

In the first part of the study, mean wheel turns (± SD) for active rats averaged 4345 ± 3586 a day for a 20-day period. In the second part of the study, average mean wheel turns for active rats increased to 8177 ± 5132 a day during the next 20-day period. As described elsewhere (16) these data show that running wheel activity increases over time. Although there was considerable between subject variability in number of wheel turns over time, individual animals showed consistent, if increasing, levels of activity.

Antinociception

Baseline tail-flick latencies did not vary as a function of running condition in either the first part of the study ([mean ± SD] active 3.69 ± 1.32 sec; sedentary 3.50 ± 0.94 sec) or the second part (active 2.89 ± 0.43 sec; sedentary 2.93 ± 0.56 sec). Baseline tail-flick latencies were not significantly different between the first and second parts of the study.

In part 1, U50,488H produced significant elevations in antinociceptive responses as a function of dose in all animals ($F(2, 28) = 5.50$; $p < 0.01$). There were no significant effects for activity levels. However, the interaction between activity condition and dose was significant ($F(2, 28) = 3.51$; $p < 0.05$) indicating that U50,488H was producing different effects in active and sedentary animals. More specifically, U50,488H produced an inverted-U-shaped dose-effect curve for sedentary animals and a virtually flat dose-effect curve for active animals (Fig. 1). Post hoc analysis yielded no further significant differences.

In part 2, 10.0 mg/kg U50,488H produced significant levels of antinociception for both groups ($F(2, 26) = 3.34$; $p = 0.05$). Post hoc analysis of time-effects showed that, at 60 min post-injection, %MPEs for active rats were significantly lower than those of sedentary rats ($t(13) = -2.22$; $p < 0.05$) (Fig. 2). There were no further significant effects for activity levels.

DISCUSSION

Long-term access to running wheels produced a decrease in U50,488H-induced antinociception. This difference was most pronounced 60 min after injection of 10.0 mg/kg of U50,488H. Although U50,488H produced significant levels of antinociception, it did not do so in a dose-dependent fashion but rather in an inverted-U-shaped dose-effect curve for sedentary animals and a virtually flat dose-effect curve for active animals. Furthermore, the peak doses of U50,488H still did

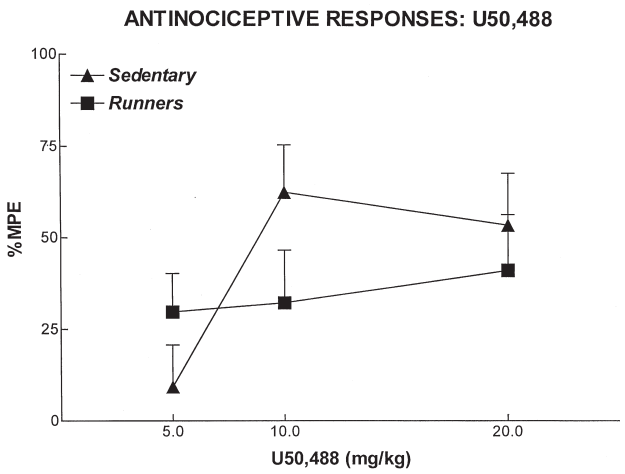

FIG. 1. Mean (± SEM) %MPEs were significantly elevated ($p < 0.05$) for all animals following cumulative dosing with U50,488H. %MPEs for active rats were significantly different ($p < 0.05$) relative to inactive rats.

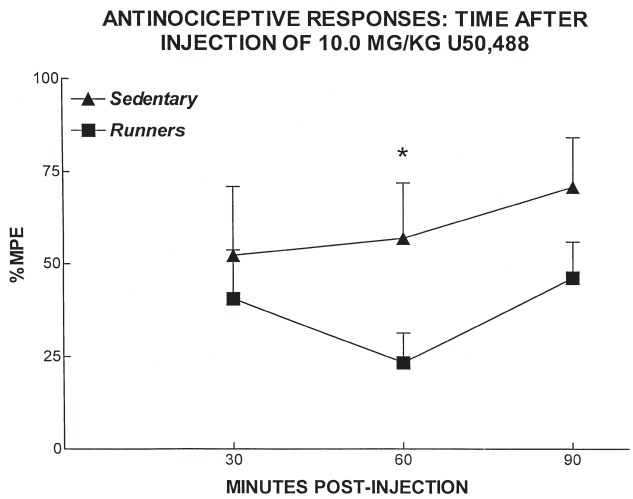

FIG. 2. Mean (± SEM) %MPEs were significantly elevated ($p < 0.05$) for all animals 30, 60, and 90 min following administration of 10.0 mg/kg U50,488H. %MPEs for active rats were significantly decreased ($p < 0.05$) relative to inactive rats. The greatest differences were evident at 60 min after injection with 10.0 mg/kg U50,488H.

not produce maximal levels of antinociception before the descending limb of the dose-effect function.

In these and related experiments it has been shown that voluntary exercise decreases the analgesic properties of opioid drugs (16). However, in the present experiments, U50,488H did not produce maximal levels of antinociception nor did it produce dose-dependent changes in antinociception. In other experiments examining the effects of a palatable diet on the analgesic potency of morphine, spiradoline or U50,488H, we demonstrated that long term intake of highly palatable sucrose solutions *enhanced* the effects of these opioid drugs (9,12,17,15,17). But, consistent with the present data, kappa-opioid agonists were much less efficacious analgesics than mu agonists. Regardless of this observation, the present experiments support and extend findings demonstrating exercise-related decreases in opiate-induced antinociception.

It should be noted that there is mounting evidence, both in human (10,11) and nonhuman subjects (2,6,7,12,16,20), for gender differences in the physiologic effects of mu- or kappa-opioid drugs. In general, the accumulated evidence suggests that mu-opioid drugs may produce greater effects in a variety of behaviors in males than in females (7,16,20, but see 2), and that kappa-opioid drugs may produce greater effects in females than in males (2,6,10,11, but see 20). In earlier experiments in our laboratory, we have shown that chronic access to running wheels significantly reduced morphine-induced antinociception in both male and female rats (16) and that males were more sensitive to the antinociceptive effects of morphine than were females. Although in the present experiments, only male rats were used, based on our previous research (16), it would be reasonable to hypothesize that female rats would also show a reduction in U50,488H antinociception following long-term access to activity-wheels. Future research is planned to address this and other questions regarding opioids, gender, and environmental variables.

In summary, rats given long-term access to running wheels showed reduced levels of kappa-opioid induced antinociception. Given that dynorphin-A is elevated in exercised rats (1), these data support and extend the hypothesis that exercise-produced elevations in endogenous opioid peptides produce cross-tolerance to exogenously administered opioid drugs. More generally, these experiments show the importance of environmental variables such as exercise on the behavioral outcome of psychoactive drugs.

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