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Effects of U50,488H on Locomotor Activity in the Hamster

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SCHNUR, P. AND J. M. WALKER. *Effects of U50,488H on locomotor activity in the hamster*. PHARMACOL BIOCHEM BEHAV **36**(4) 813–816, 1990.—Two experiments investigated the effects of the specific kappa opiate agonist, U50,488 on locomotor activity in the golden Syrian hamster. In Experiment 1, the effects of U50,488 were found to be dose-related, with a 1 mg/kg dose eliciting hyperactivity and a 10 mg/kg dose eliciting hypoactivity. In Experiment 2, the dual effects of U50,488 on locomotor activity were shown to be naloxone (1 mg/kg) reversible. It is suggested that the effects of U50,488 on activity are consistent with the reported dual opposing influences of kappa agonists in the substantia nigra pars compacta and pars reticulata.

U50,488H Hamster Kappa opiates Opiates Locomotor activity

OPIATES produce their myriad biochemical, physiological and behavioral effects by acting on one or more specialized receptors. The existence of multiple opiate receptors has been recognized since the mid-1970's (9, 16, 18) and three types of opiate receptors, mu, delta and kappa, are acknowledged to exist in brain (1, 16–18, 31). Accumulating evidence indicates that the mu receptor is associated with increases in activity in the rat [e.g., (13, 27, 31)], whereas the kappa receptor is associated with decreases in activity in both rats and mice (4, 5, 7, 12, 18, 21, 29, 31). The purpose of the present experiments was to investigate the locomotor effects of the kappa agonist, U50,488, in the hamster.

The locomotor effects of the mu agonist morphine are similar in both rat and hamster. In both species, morphine's effects on locomotor activity are characterized by biphasic dose-effect and time-effect functions: Compared with saline controls, low doses of morphine elicit hyperactivity, whereas high doses elicit hypoactivity. Across a wide range of moderate to high doses, an initial period of hypoactivity is followed by hyperactivity (3,23).

To date, there have been no studies of the effects of kappa agonists in the hamster. On the basis of the similarity of the effects of morphine in the two species, one might speculate that kappa agonists too would have similar effects. On the other hand, since there is evidence to suggest that kappa receptors are predominant in the hamster brain, whereas mu receptors are predominant in the rat brain (20,32), it is plausible that the functional significance of these receptors might differ in the two species. In the experiments reported here, we tested the effects of U50,488H [trans-(±)-3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl)-benzeneacetamide methane sulfonate], a highly specific agonist at the kappa receptor with little activity at mu and delta receptors (15, 28, 29).

METHOD

Subjects

Thirty-two female golden Syrian hamsters, *Mesocricetus auratus*, approximately 149 days old with a mean weight of 144 g, were used in Experiment 1. In Experiment 2, thirty-two female hamsters, approximately 107 days old with a mean weight of 119 g, were used. All hamsters were housed singly in stainless steel wire mesh cages with free access to food and water except as indicated above. They were maintained on a 12:12-hr light-dark cycle (lights on at 0700) in a temperature-controlled vivarium. All experiments were conducted during the light phase and without regard to the four-day estrous cycle of the hamster.

Apparatus and Materials

The apparatus consisted of 32 activity wheels (Wahmann, Model LC-34). Each wheel sat in a plywood enclosure that isolated the wheels visually from one another. The enclosures were open on one side and the noise from ventilator fans in each enclosure (approximately 70 dB SPL) provided some degree of auditory masking. Movements of each wheel were detected by microswitches, transduced by an interface (Lafayette, Model 1180-01) and recorded on Apple II plus computers. U50,488H (Upjohn) and naloxone HCl (Sigma) were diluted in 0.9% saline. All doses refer to the salt and all injections were given intraperitoneally (IP) in 1 ml/kg volumes.

Procedure

Experiment 1. On Days 1–3, animals were given an IP injection of saline and placed in the running wheels 10 min later

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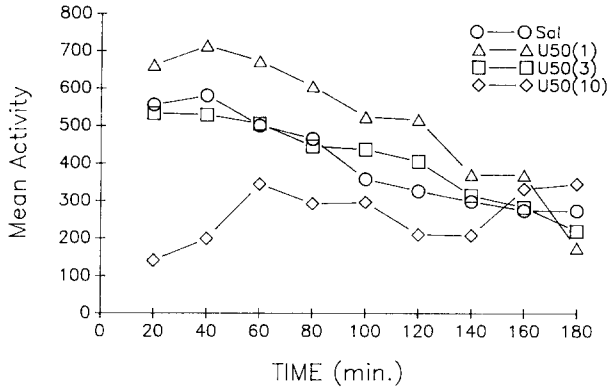

FIG. 1. Mean activity as a function of time for groups given different doses of U50,488 (0, 1, 3 or 10 mg/kg, IP) in Experiment 1.

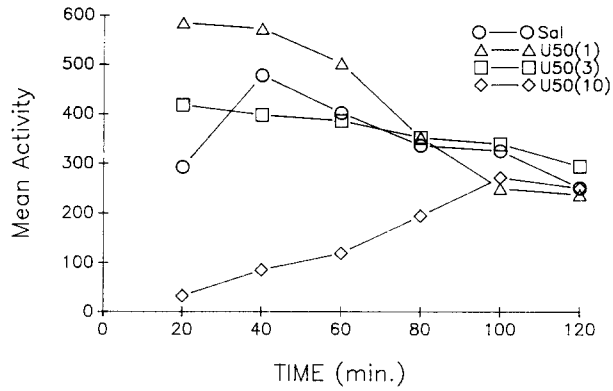

FIG. 2. Mean activity as a function of time for groups given different doses of U50,488 (0, 1, 3 or 10 mg/kg, IP) following a saline preinjection in Experiment 2.

for a three-hr baseline session. The purpose of these sessions was to acclimate the animals to the running wheels as well as to the handling and injection procedures. On Day 4, animals were randomly assigned to one of four groups and were given an IP injection of one of four doses of U50,488H [0 (saline), 1, 3 and 10 mg/kg]. Ten min later they were placed in the running wheels for a three-hr test session. The number of wheel revolutions every 20 min was recorded.

Experiment 2. The procedures for Experiment 2 were identical to those of Experiment 1 except that 1) sessions were two hr in length, and 2) on the test day animals were given a series of two IP injections 10 min apart. The shorter test session was suggested by the results of Experiment 1, wherein differences among groups were absent after two hours. Eight groups (n=4), roughly matched on activity during baseline sessions, were randomly assigned to drug treatments created by the factorial combination of the first (saline or 1 mg/kg, naloxone) and the second injection (0, 1, 3 or 10 mg/kg, U50,488H).

RESULTS

Experiment 1

Figure 1 shows mean activity as a function of time for all groups in Experiment 1. The effects of U50,488 on running wheel activity were dose-related. Compared with saline controls, animals given a 1 mg/kg dose of U50,488 were hyperactive and animals given a 10 mg/kg dose of U50,488 were hypoactive for approximately two hours. After two hours, differences among groups had dissipated. A dose of 3 mg/kg of U50,488 had no effect on running wheel activity. A 4 (Dose) × 9 (Time) mixed factorial ANOVA indicated that the effects of time, $F(8,224)=19.76$, $p<0.001$, and the Dose × Time interaction, $F(24,224)=5.52$, $p<0.001$, were significant. Post hoc comparisons using Fisher's LSD test (14) indicated that animals given a 1 mg/kg dose of U50,488 were significantly more active than saline controls at 40–120 min of the test session ($p<0.05$). Similarly, animals given a 10 mg/kg dose of U50,488 were significantly less active than saline controls for the first 80 min of the test session and again at 120 min ($p<0.05$).

Experiment 2

Figure 2 shows mean activity as a function of time for groups given a saline preinjection in Experiment 2. It can be seen that, as in Experiment 1, the effects of U50,488 on activity were dose-related, with the 1 mg/kg dose eliciting hyperactivity and the 10 mg/kg dose eliciting hypoactivity, compared with saline controls. Again, the 3 mg/kg dose had no discernible effect on activity. Figure 3 shows mean activity as a function of time for groups given a naloxone preinjection in Experiment 2. Naloxone effectively blocked U50,488-elicited hyperactivity and hypoactivity. That is, in animals given a naloxone preinjection, a 1 mg/kg dose of U50,488 failed to elicit hyperactivity and a 10 mg/kg dose of U50,488 failed to elicit hypoactivity. Among animals given a naloxone preinjection, however, a 3 mg/kg dose of U50,488 elicited hypoactivity after 100 min and all doses of U50,488 elicited hypoactivity after 120 min.

A 2 (Preinjection) × 4 (Dose) × 6 (Time) mixed factorial ANOVA indicated that the effect of time was significant, $F(5,120)=6.21$, $p<0.001$. In addition, the interaction between dose and time, $F(15,120)=2.65$, $p<0.001$, and the interaction among preinjection, dose and time, $F(15,120)=1.81$, $p<0.05$, were significant. Post hoc comparisons using Fisher's LSD test ($p<0.05$) indicated that following a saline preinjection, animals given a 1 mg/kg dose of U50,488 were hyperactive for the first 20 min of the test session and those given a 10 mg/kg dose of U50,488 were hypoactive for the first 60 min of the test session compared with saline controls. In animals given a naloxone preinjection, differences among groups were absent until 100 min of the test: at 100 min, Group U50,488 (3 mg/kg) was hypoactive compared with saline controls and, at 120 min, all groups were

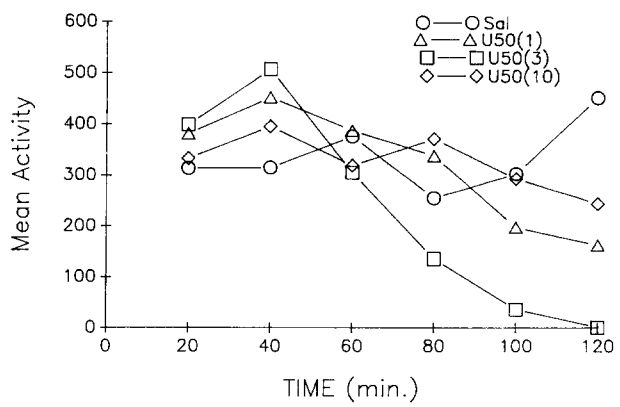

FIG. 3. Mean activity as a function of time for groups given different doses of U50,488 (0, 1, 3 or 10 mg/kg, IP) following a naloxone preinjection in Experiment 2.

hypoactive compared with saline controls. This delayed hypoactivity produced by all doses of U50,488 among naloxone-preinjected animals is puzzling and unexplained at present.

DISCUSSION

The present experiments reveal that, in the hamster, low doses of U50,488 elicit hyperactivity, whereas high doses elicit hypoactivity. Since both U50,488-elicited hypoactivity and hyperactivity were antagonized by naloxone in Experiment 2, it is likely that the effects were mediated by opiate receptors. Moreover, since U50,488 is highly specific for the kappa opiate receptor (15, 28, 29), it is likely that both effects were mediated by kappa receptors. Since there appears to be more than one type of kappa receptor (2, 6, 11, 33), it is possible that hypoactivity and hyperactivity are mediated by different kappa receptor subtypes. For example, U50,488 binds to both $kappa_1$ and $kappa_2$ receptors, with K_is of approximately 2.4 nM and 484 nM, respectively (33). Perhaps the high-affinity site mediates hyperactivity elicited by low doses and the low-affinity site mediates hypoactivity elicited by high doses. Under this hypothesis, one might explain the lack of effect of the 3 mg/kg dose of U50,488 on activity as due to the algebraic summation of excitatory (hyperactivity) and inhibitory (hypoactivity) influences.

Alternatively, U50,488 acting at a single kappa receptor type might produce different effects depending upon the neuroanatomical localization of kappa receptors. A high dose of U50,488 might reach a different population of kappa receptors than a low dose. The substantia nigra (SN) has been proposed as a possible site of action for the dual opposing effects of kappa agonists in the rat (26). It has been proposed (26) that kappa agonists exert locomotor inhibition through dopamine neurons in the SN pars compacta (SNC) and locomotor excitation through nondopaminergic neurons in the SN pars reticulata (SNR). Systemic injections of U50,488 lead to a decrease in the firing rate of DA cells in the SNC (30), a decreased release of striatal DA and a concomitant inhibition of locomotor activity (7). By contrast, kappa agonists microinjected unilaterally into the SNR produce dopamine-independent locomotor activation, as indexed by contralateral circling (8,19). Since the predominant action of kappa agonists in the SNR is a decrease in cell firing rate and since the SNR exerts an inhibitory GABAergic influence on its targets, it is likely that locomotor activation is the result of disinhibition (26).

In the rat, U50,488-elicited hyperactivity has not been reported. Additional research will be required to determine whether this represents an important species difference in the response of rats and hamsters to U50,488 or simply a procedural difference between the present experiments and those using rats; for example, the use of running wheel activity in the hamster versus open field measures of activity in the rat. In one investigation using open field measures of locomotion in the rat, a trend towards increased locomotion and rearing duration was reported following a low dose (0.1 mg/kg) of U50,488 (12). The fact that the hamster brain is relatively rich in kappa receptors compared with that of the rat (20,32) encourages the hypothesis that behavioral differences in the response to U50,488 might be understood in terms of the number and/or distribution of kappa receptors in the brain. Direct comparison of the effects of U50,488 in rats and hamsters under comparable experimental conditions should be undertaken.

The effects of U50,488 on hamster locomotor activity also invite comparison with the effects of morphine on hamster locomotor activity. Like U50,488, morphine elicits naloxone-reversible hyperactivity at low doses and naloxone-reversible hypoactivity at high doses (22). Since morphine acts as an agonist at both mu and kappa receptors (20), it is possible that morphine-elicited hypoactivity is mediated, to some extent, by actions at kappa receptors. Recall that selective mu agonists elicit hyperactivity in the rat (13, 27, 32). Cross-tolerance experiments between U50,488 and morphine would be informative [cf. (10,24)], as would experiments testing the effects of specific kappa antagonists [e.g., nor-binaltorphimine; (25)] on morphine-elicited activity in the hamster. Unlike U50,488, morphine elicits a biphasic time effect curve. That is, compared with saline controls, moderate and high doses of morphine elicit an initial period of hypoactivity followed by hyperactivity. In the present experiments, U50,488-elicited hypoactivity was not followed by hyperactivity. Rather, hypoactivity was followed by a return to the activity level of saline controls. Although a longer test session might have revealed compensatory hyperactivity following a 10 mg/kg dose of U50,488, Figs. 1 and 2 suggest that activity levels were at or near asymptote after 2–3 hours and thus unlikely to have changed subsequently. Nevertheless, future research should make direct comparisons of the effects of morphine and U50,488 on activity in suitably long test sessions to test the hypothesis that the mechanisms underlying morphine-elicited hypoactivity are distinguishable from those underlying U50,488-elicited hypoactivity.

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