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BRIEF COMMUNICATION

Morphine Tolerance and Sensitization in the Hamster

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SCHNUR, P *Morphine tolerance and sensitization in the hamster.* PHARMACOL BIOCHEM BEHAV 22(1) 157–158, 1985 —The effects of morphine on hamster locomotor activity were studied Repeated administration of morphine in doses from 5 to 40 mg/kg produced systematic changes in morphine's biphasic time effect pattern: morphine's sedative effects decreased (tolerance) while morphine's excitatory effects increased (sensitization) These results extend findings of behavioral tolerance and sensitization in the hamster to a range of higher doses than those used previously

Tolerance Sensitization Morphine Hamsters

MORPHINE has biphasic effects on locomotor activity in hamsters. compared with saline controls, morphine produces a dose-related decrease in activity, a gradual dose-related recovery and finally, a period of sustained hyperactivity [5,6]. Furthermore, at low doses (0.5, 1.0, 2.5, and 5.0 mg/kg), the repeated administration of morphine produces two changes in the biphasic pattern: a decrease in the initial hypoactivity (i.e., tolerance) and an increase in the subsequent hyperactivity (i.e., sensitization) [5]. The present work was designed to determine whether similar changes occur at higher doses than those used previously Accordingly, hamster locomotor activity was monitored for three hours on 14 successive days following morphine administration at doses of 5, 10, 20 and 40 mg/kg

METHOD

Subjects

Forty adult golden Syrian hamsters (23 males, 17 females), with a mean weight of 109 grams were used. The hamsters were descended from animals obtained from Sasco, Inc. (Omaha, NE).They were housed individually, maintained on a 12:12 hour light-dark cycle, and given free access to food and water throughout the experiment

Apparatus and Materials

The apparatus consisted of eight identical activity wheels (Wahmann Co , Model LC-34) which were housed in a room dimly illuminated by two 15 watt bulbs. Running wheels were fitted with microswitches and interfaced to Canon printing calculators (Model TP-8), modified [3] to record the number of wheel revolutions. An ambient noise level of 79 dB (re:0.0002 dynes/cm^2, A scale) was maintained by a Lafayette white noise generator (Model 15800).

Morphine injections consisted of 5, 10, 20, or 40 mg/kg doses of morphine sulfate, expressed as the salt, dissolved in 1 ml of 0.9% saline. Morphine and saline injections were administered in 1 ml/kg volumes

Procedure

Experimental procedures were conducted on seventeen consecutive days. On the first three days, animals were injected with saline and placed in the running wheels for a three hour baseline session. Baseline sessions served to accustom animals to the running wheel and to the injection procedure. Animals were then randomly assigned to the five treatment conditions (n=8) defined by morphine dose (0, 5, 10, 20, 40 mg/kg of morphine sulfate). During the next 14 days, animals received daily injections of either saline (Group SAL) or a dose of morphine sulfate (Groups MS-5, MS-10, MS-20 and MS-40).

Daily procedures were as follows: animals were weighed, given a subcutaneous injection of saline or morphine in the dorsal surface of the neck and, following a 15 minute interval, placed in the running wheels for three hours. The number of wheel revolutions was recorded at 20 minute intervals for each animal.

RESULTS AND DISCUSSION

Figure 1 shows the effects of morphine as a function of time for all groups. Time-effect curves for the first three days and for the last three days of morphine administration are shown in the top and bottom panels of Fig. 1, respectively. Morphine's biphasic effects on locomotor activity were evident on the first three days: compared with saline controls, morphine produced an initial dose-related decrease in locomotor activity, followed by a dose-related rate of recovery, and in all but Group MS-40, recovery was followed by a period of hyperactivity. Previous work in our laboratory [6], has established that hyperactivity occurs even with doses as high as 40 mg/kg, though it is manifested in longer

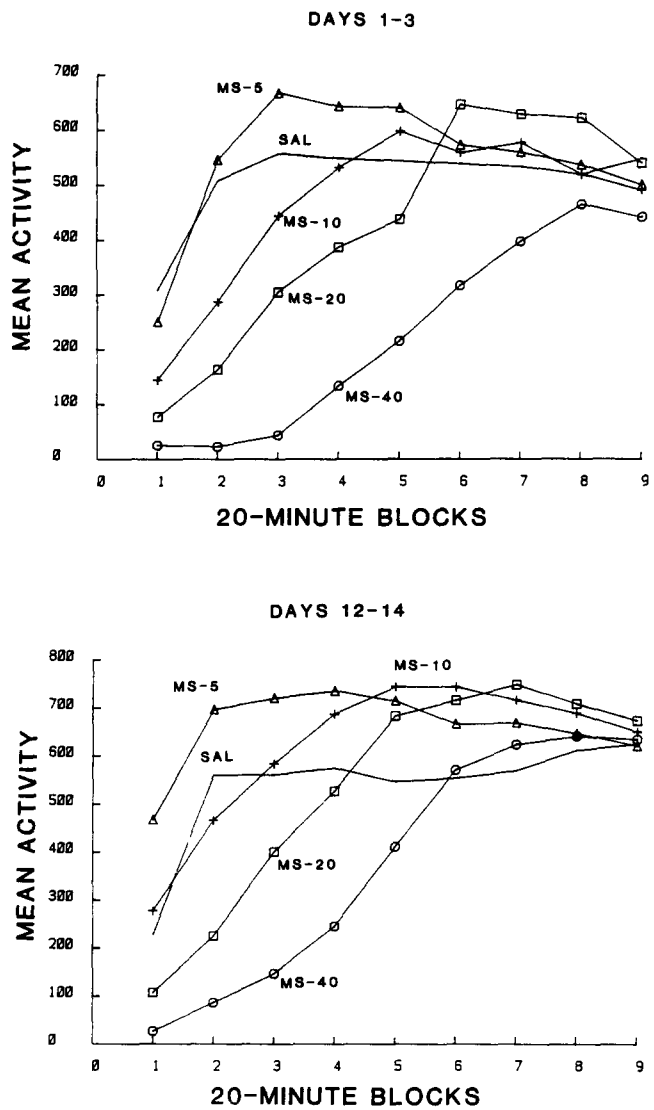

FIG 1 Top panel shows mean activity (number of wheel revolutions) on the first three morphine days as a function of 20-minute blocks of time for all drug treatment groups (n=8) Bottom panel shows mean activity for those same groups on the last three morphine days as a function of 20-minute blocks of time

test sessions than those employed here. On Days 12–14, two changes were apparent in morphine's time-effect pattern. First, the magnitude and duration of the initial sedation decreased (i e., tolerance), note, for example, the absence of sedation in Group MS-5 Second, the magnitude and duration of the hyperactivity increased (i e., sensitization), note, for example, the hyperactivity in Group MS-40 The time-effect curve for Group SAL is stable between the first and last three days of testing. By contrast, at each morphine dose, tolerance to morphine elicited sedation as well as sensitization to morphine elicited excitation can be seen A 9 (Time Blocks) × 14 (Days) × 5 (Morphine Dose) mixed factorial analysis of variance (ANOVA) of locomotor activity corroborates these conclusions The effects of time blocks, $F(8,280)=88\ 10$, $p<0\ 001$, days, $F(13,455)=10\ 18$, $p<0\ 001$, and morphine dose, $F(4,35)=5\ 43$, $p<0\ 002$, were all significant In addition, the interaction between morphine dose and time blocks was significant, $F(32,280)=10.24$, $p<0\ 001$

The present study extends our investigation of the effects of morphine on locomotor activity in the hamster Previously, we reported that the repeated administration of morphine in doses of 0 5, 1 0, 2 5 and 5 0 mg/kg produced tolerance to morphine's sedative effects and sensitization to morphine's excitatory effects [5] It can now be said that parallel changes are evident at doses ranging up to 40 mg/kg That is, daily morphine injections led to a decrease (i e , tolerance) in sedation and an increase (i e , sensitization) in hyperactivity at all doses Moreover, at the lowest dose tested, hyperactivity replaced sedation as the initial response to morphine after fourteen days of treatment In the research using 0 5–5 0 mg/kg doses of morphine, we found that hyperactivity replaced sedation as the initial response to morphine after as few as three days of drug administration

Similar changes following chronic morphine administration have been described for locomotor activity in rats [1,4]. Moreover, Babbini *et al* [2] reported that following chronic treatment with a 20 mg/kg dose of morphine, hyperactivity replaced sedation and delayed hyperactivity was detectable following a nontreatment interval of 8 months Thus, under some circumstances, changes in morphine's effects can be quite durable Finally, it should be noted that, in the present context, the use of the terms tolerance and sensitization is purely descriptive and is not intended to imply anything specific about underlying mechanisms

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