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Locomotor Activity in Morphine-Dependent and Post-Dependent Rats[1,2]

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BRADY, L. S. AND S. G. HOLTZMAN. *Locomotor activity in morphine-dependent and post-dependent rats.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 361–370, 1981.—The effects of morphine and naloxone were compared on the locomotor activity of nondependent, morphine-dependent, and post-dependent rats. Dependence was induced and maintained for 30 weeks by scheduled access to 0.05% morphine solution for 10 min every 6 hr. Locomotor activity in nondependent and dependent animals was increased by low doses of morphine and reduced by higher doses. Both components were antagonized by naloxone. Chronic morphine treatment produced marked tolerance to the depressant effect of high morphine doses, but not to the stimulant effect of low doses. Post-dependent animals remained tolerant to the depressant effect of high doses of morphine. The development of tolerance to the depressant but not to the stimulant effect of morphine in dependent and post-dependent animals suggests that different neuronal substrates mediate morphine-induced stimulation and depression of locomotor activity. Abrupt or naloxone-precipitated withdrawal generally disrupted locomotor activity in dependent rats. Naloxone alone also decreased activity in post-dependent animals. Thus, chronic morphine administration produces long-lasting changes in the sensitivity of dependent and post-dependent rats to the effects of morphine and naloxone on locomotor activity.

Locomotor activity Morphine Naloxone Physical dependence Tolerance Withdrawal

MORPHINE has complex effects on the locomotor activity of rats. These effects include mixed depressant and stimulant components of action that are time- and dose-related. Low to moderate doses of morphine (i.e., 1.0–5.0 mg/kg) produced an initial excitation lasting one to two hours followed by a return to normal motor activity [2, 3, 6, 8]. Higher doses (i.e., 10–40 mg/kg) have biphasic effects: an initial depression of locomotor activity is followed by a period of hyperactivity [3, 6, 8, 19]. The duration of the depressant effect increases as a function of the dose of morphine [8].

The effects of morphine on locomotor activity are markedly altered in rats that are chronically treated with morphine. In tolerant and dependent rats, the morphine dose-effect curve is shifted to the right relative to the curve in nondependent rats so that much larger doses of morphine are necessary to produce depressant and stimulant actions [3,21]. At high doses of morphine, the initial depression of locomotor activity is relatively transient and the later increase in activity is enhanced [3,21].

Chronic treatment with morphine results not only in numerous physiological and behavioral changes during the period of dependence, but also in persistent changes that are evident long after morphine treatment has been terminated. Significant elevations in the body temperature and metabolic rate of rats have been reported for as long as six to twelve months after the acute phase of morphine withdrawal [16]. There is also evidence that the effects of morphine on locomotor activity are modified in rats that have been formerly dependent on morphine. Six to seven weeks after morphine withdrawal, morphine produces a prominent increase in the locomotor activity of rats at a dose, 10 mg/kg, that markedly decreases activity in morphine-naive rats [18]. As long as eight months after the termination of chronic morphine treatment, complete tolerance to the initial depressant effect of 20 mg/kg of morphine on motor activity is still evident; the responses of these animals to the delayed excitatory effects of morphine remains unchanged [4].

Few studies have systematically compared the behavioral effects of morphine in post-dependent rats with those in morphine-dependent and nondependent rats. We recently evaluated the effects of morphine and naloxone, a pure narcotic antagonist, on food-reinforced responding in the same group of rats before, during, and after chronic morphine administration [5]. Chronic morphine treatment produces a three-fold increase in the ED_{50} of morphine for decreasing response rate (i.e., tolerance) and a dramatic increase in the effectiveness of naloxone for decreasing response rate, probably as a consequence of the precipitation of withdrawal. The altered sensitivity of dependent rats to morphine and naloxone is completely reversed in post-dependent rats tested four to twelve weeks after the withdrawal of morphine.

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TABLE 1
TIME SEQUENCE OF EXPERIMENTS*

Weeks	Drinking Solution†	Tests
1–11	0.05% morphine	none
12	0.05% morphine	habituation
13–16	0.05% morphine	morphine (0.1–30 mg/kg) or saline
"dependent stage"		
17–20	0.05% morphine	morphine (0.3–100 mg/kg) + naloxone (0.3 mg/kg) or saline
21–23	0.05% morphine	naloxone (0.003–3.0 mg/kg) or saline
24–27	0.01% quinine	withdrawal
28–31	0.05% morphine	time course: morphine (3.0, 30 mg/kg) or saline
32–37	0.01% quinine	none
38	0.01% quinine	habituation
39–42	0.01% quinine	morphine (0.1–30 mg/kg) or saline
"post-dependent stage"		
43–46	0.01% quinine	naloxone (0.003–3.0 mg/kg) or saline
47–50	0.01% quinine	time course: morphine (3.0, 30 mg/kg) or saline

*Morphine-treated animals were tested on Tuesdays and Fridays; nondependent animals were tested on Mondays and Thursdays.

†Morphine-treated animals were given scheduled access to morphine and free access to quinine; nondependent animals were given free access to water.

In view of the reversibility of the effects of morphine and naloxone on response rate of formerly dependent rats and because of the fragmentary nature of the existing data on the effects of these drugs on the locomotor activity of post-dependent rats, this investigation was undertaken in order to systematically compare the effects of morphine, as well as naloxone, on the locomotor activity of morphine-dependent and post-dependent rats, and nondependent rats that had not been physically dependent. Morphine dependence was induced and maintained by giving the animals scheduled access to a morphine solution which was their only source of fluid [9]. With this procedure, tolerant and dependent animals remained healthy throughout a 30-week period of chronic morphine administration.

METHOD

Animals

The subjects were 16 male CFE rats (300–350 g) obtained from Charles River Breeding Laboratories (Wilmington, MA) at 110 to 115 days of age.

Upon arrival from the supplier, the rats were randomly separated into two groups of eight and designated to be either morphine-treated or nondependent animals. The morphine-treated animals were housed singly in cages that were placed in a specially constructed cabinet designed to permit control over the access of each animal to its drinking solution [9]. Food (Purina Rat Chow) was available ad lib. The cabinet was continuously ventilated by two small blower units and was illuminated between 7:00 a.m. and 7:00 p.m. by 20 W fluorescent light bulbs located 20 cm above the cage tops of each shelf. The nondependent animals were housed in group cages, two to a cage, and maintained on a 12-hr light-dark cycle with continuous access to food and water.

Morphine Treatment

Morphine tolerance and dependence were induced and maintained in the morphine-treated animals by scheduled access to morphine drinking solutions. This procedure has been described in detail [9]. Briefly, bottles containing 0.05% morphine solution (base concentration) were placed in racks positioned above the home cage of the rats so that the drinking spouts could be rotated into and out of the cages by turning the rack through a 30° arc. The racks were turned by a low rpm motor which was controlled by electromechanical programming equipment.

The morphine-treated animals were given ten min access to the morphine solution every six hr, beginning at 6:00 a.m. Daily morphine intake was monitored two times a week by weighing the drinking bottles after the 6:00 a.m. access period on Mondays and Tuesdays and on Thursdays and Fridays. It was assumed that a change in weight of 1.0 g between weighings was equivalent to 1.0 ml of solution consumed.

Apparatus

Locomotor activity was measured on two-channel Electronic Activity Monitors which were connected by shielded cable to electromagnetic sensors (31404 and SA1566, respectively, Stoelting Co., Chicago, IL). The activity chamber was a standard polycarbonate rat cage (51×41×22 cm) that was covered with a wire top and centered upon the sensor platform. The activity cage and sensor were housed in a ventilated, sound-attenuating chamber that was illuminated by a 6 W fluorescent light bulb located eight cm above the cage top.

The counting thresholds were individually adjusted for each sensor. One channel was calibrated with a swinging

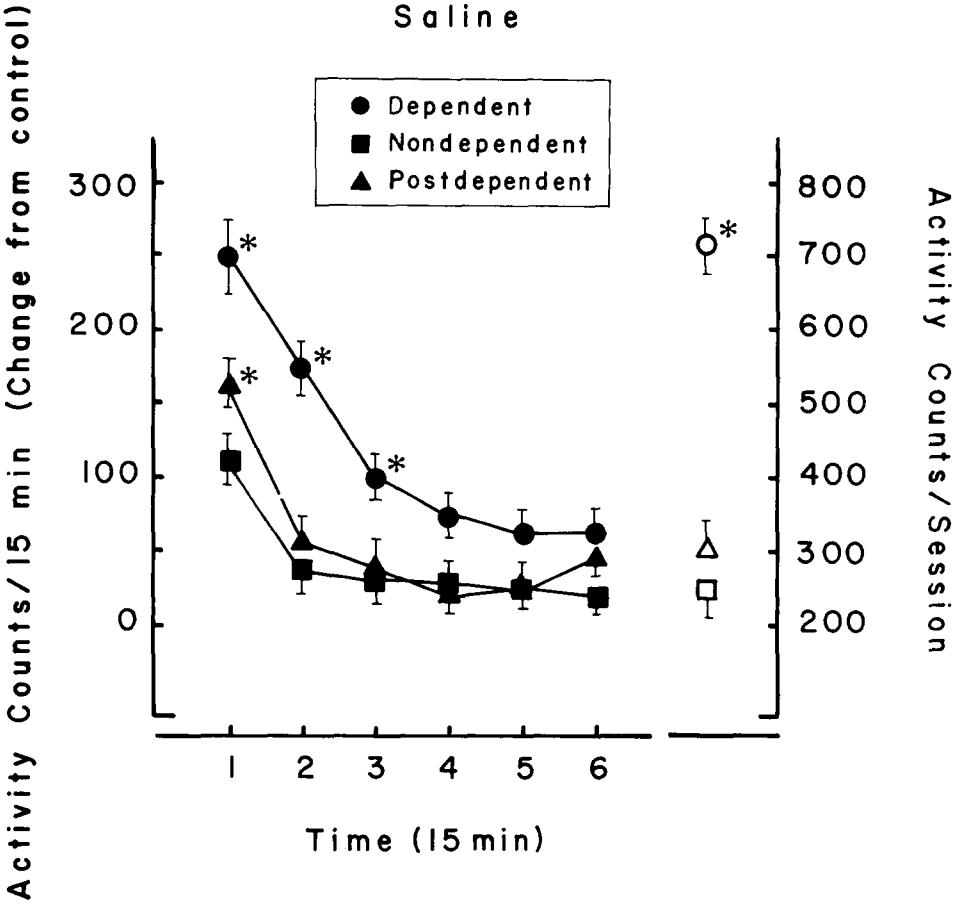

FIG. 1. The spontaneous activity of nondependent, morphine-dependent and post-dependent rats during successive 15-min segments of a 90-min test session and the total activity counts/session (open points) following saline administration. In this and all subsequent figures, each point represents the mean and SEM of eight independent determinations. The symbol (*) indicates a significant difference from nondependent rats, $p<0.01$.

pendulum to measure gross motor movements which closely corresponded to locomotor activity. Counts for each sensor were cumulatively recorded every 15 min by digital printers (Grason Stadler Co., West Concord, MA).

Procedure

The 16 animals were tested in two contiguous stages over a 12-month period. In the first stage (dependent) the morphine-treated group had scheduled access to morphine solution. In the second stage (post-dependent) the animals were removed from the cabinet and placed in group cages, two per cage. The animals were given free access to quinine solution (0.01%) in order to minimize the alterations in drinking patterns that might occur when morphine is removed from the drinking solution.

After the dependent animals had been exposed to the regimen of scheduled access to morphine solution for 11 weeks, both groups of rats were habituated to the activity chambers in five daily 90-min sessions. Drug testing began at this point. Animals were injected SC with either drug or isotonic saline in a volume of 1.0 ml/kg of body weight. Five minutes after the injection, the animals were placed singly in the test chambers and activity was monitored for a 90-min period. Dependent animals were tested on Tuesdays and Fridays; nondependent rats were tested on Mondays and Thursdays. All test sessions were conducted between 7:00 a.m. and 12:00 a.m., which was one to six hr after the last morphine access period for the dependent group.

The sequence of experiments is presented in Table 1. The order of doses and saline were randomized within each drug series. Dose-effect curves for morphine, naloxone, and morphine plus naloxone were determined in the dependent and nondependent animals. In order to examine the effect of abrupt withdrawal of morphine on locomotor activity, dependent rats were placed in the activity chambers for a 72-hr period beginning immediately after the 12:00 a.m. access period on Friday. The rats were given free access to food and quinine solution, and a 12-hr light-dark cycle was maintained. The animals were returned to the cabinet on Monday and were given scheduled access to morphine at the 12:00 a.m. access period. Testing was resumed two to three weeks later. The nondependent animals were also tested for a similar 72-hr period with continuous access to food and water.

After completion of testing in the dependent stage, morphine was removed from the drinking solution and replaced by quinine. Six weeks later, testing was resumed in the now post-dependent and the same nondependent rats; dose-effect

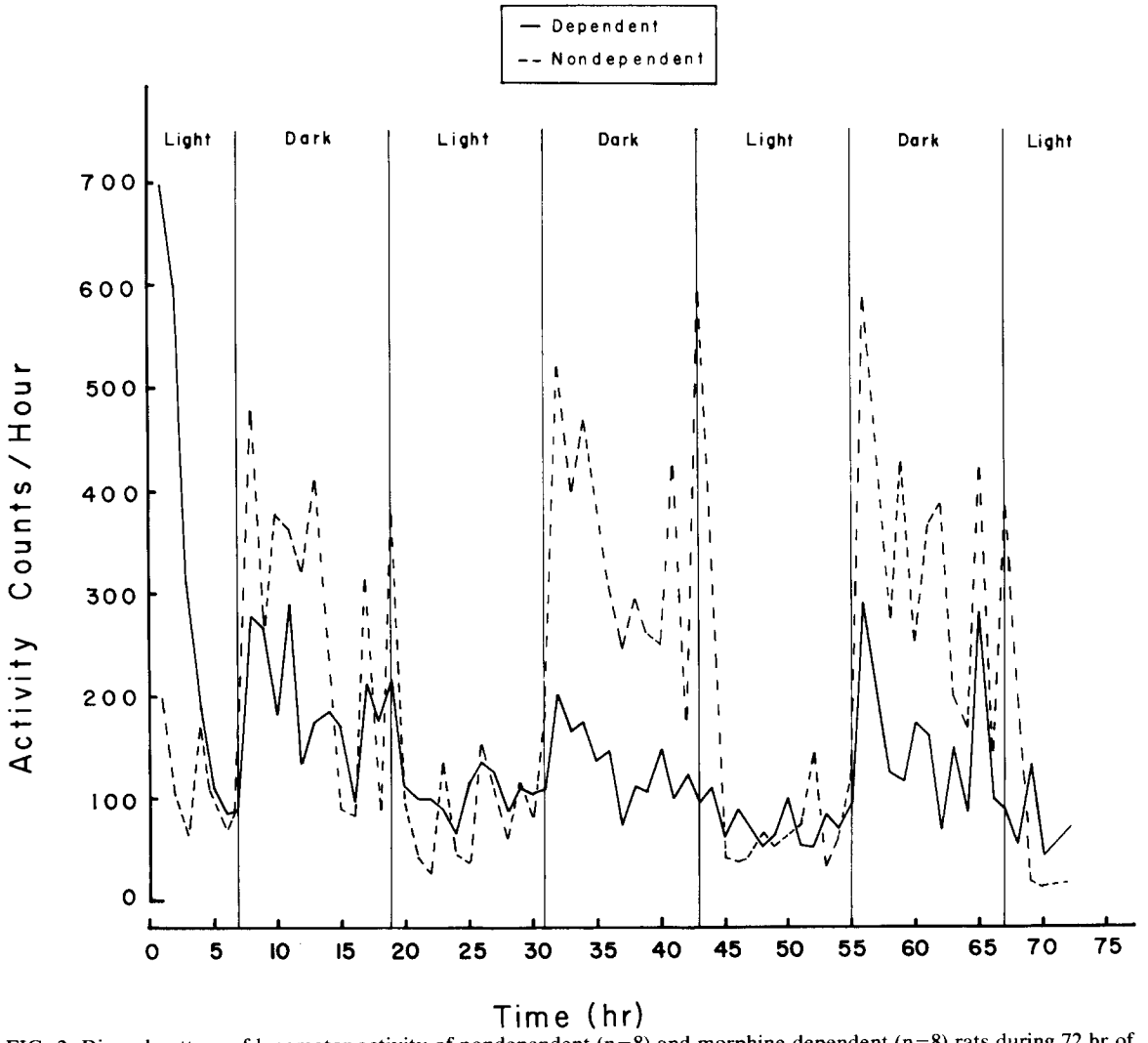

FIG. 2. Diurnal pattern of locomotor activity of nondependent (n=8) and morphine-dependent (n=8) rats during 72 hr of morphine withdrawal. Quinine was substituted for morphine in the drinking solution of dependent rats at time zero. Vertical lines indicate the onset of consecutive 12 hr light-dark periods. Note the initial elevation of activity in the dependent animals and the marked suppression of activity during the subsequent dark periods.

curves for morphine and naloxone and time-effect curves for morphine were redetermined at this time (Table 1).

Drugs

The drugs used in this study were morphine sulfate (S. B. Penick Co., Newark, NJ) and naloxone hydrochloride (National Institute on Drug Abuse). All drugs were dissolved in 0.9% saline and administered SC. Drug doses and concentrations are expressed in terms of the free base.

Data Analysis

In order to facilitate comparisons between the morphine-treated and nondependent rats, data are usually expressed as the difference in activity counts/session following drug and saline administration for individual animals in each stage of the study. The dose-effect and time-effect curves were compared in the dependent and nondependent rats and in the post-dependent and nondependent rats by a two-way analysis of variance with repeated measurements. Individual dose and time points were compared by orthogonal t-tests on the treatment sums. A p value of less than 0.01 was taken as the level of statistical significance. Data are presented as means ± SEM.

RESULTS

Morphine Consumption

The mean daily morphine consumption of individual animals was measured beginning 11 weeks after administration of the drug. The average group intake of the dependent rats was 42 ± 1.4 mg/kg/day and remained stable during the 12-week period of testing. Average daily intake of individual animals ranged from 37 ± 1.2 to 47 ± 0.8 mg/kg.

Baseline Locomotor Activity

Locomotor activity is presented in successive 15-min intervals for a 90-min session following an injection of saline in

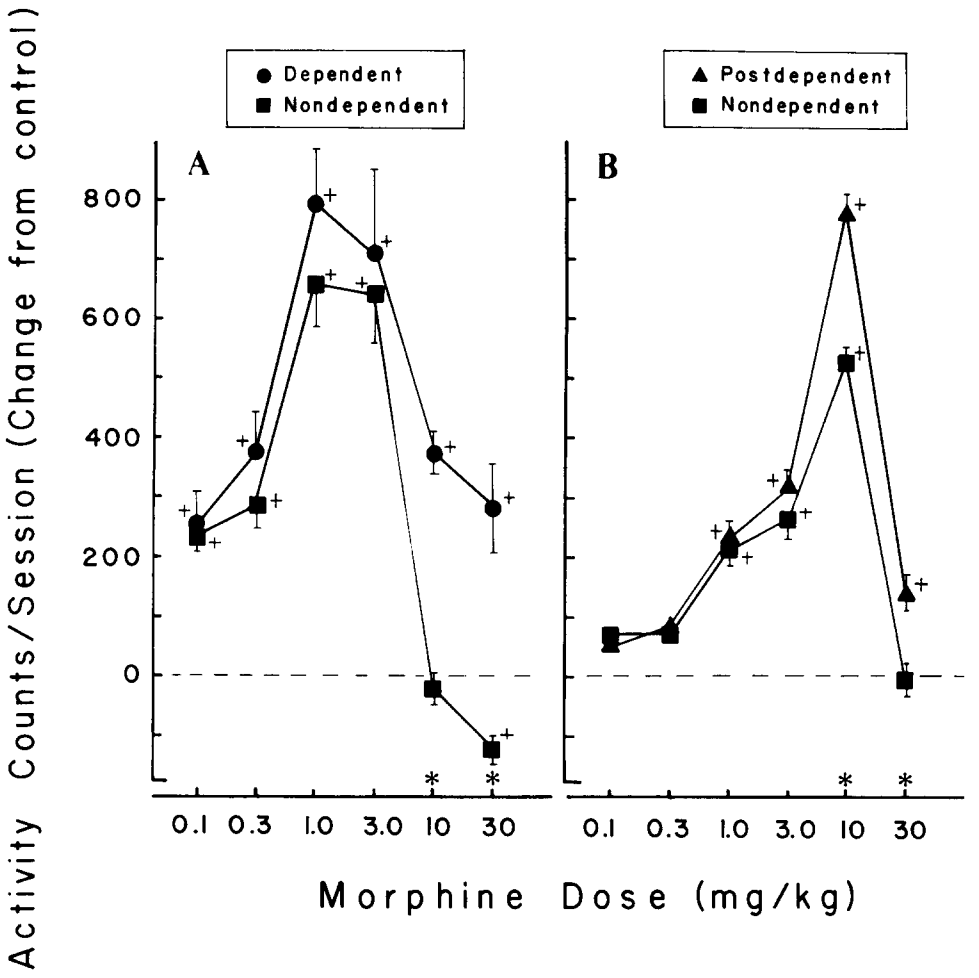

FIG. 3. Dose-response curves for the effects of morphine on locomotor activity in dependent and nondependent rats (A), and six to ten weeks after morphine withdrawal, in post-dependent and non-dependent rats (B). The symbols (+ and *) indicate differences from baseline and from nondependent rats, respectively, $p<0.01$. Absolute baseline activity counts for nondependent, dependent and post-dependent rats are 250 ± 25, 700 ± 50 and 300 ± 30, respectively.

nondependent, morphine-dependent, and post-dependent rats (Fig. 1). The same rats comprise the dependent and post-dependent groups, the latter being tested six to ten weeks after the withdrawal of morphine. The activity of the nondependent rats was very low and did not vary during the 12-month period of testing. The total activity of the dependent rats during the 90-min session was more than twice that of the nondependent rats (Fig. 1). However, six to ten weeks after withdrawal, the locomotor activity of the now post-dependent rats had returned to essentially the same levels as that of the nondependent animals, being significantly elevated only during the first 15 min of the session.

Diurnal Pattern of Activity

Morphine was removed from the drinking solution of the dependent rats after 24–27 weeks and the locomotor activity of these animals was compared to the activity of nondependent rats during a 72-hr period (Fig. 2). The nondependent rats showed a typical diurnal pattern of activity, in which activity increased during the dark phase of the light-dark cycle and decreased during the light phase. In contrast, the activity of dependent animals, which was initially much higher than that of the non-dependent rats, decreased rapidly and remained relatively depressed throughout the three dark periods of the 72-hr test. Maximal suppression of activity appeared to occur during the second dark cycle, 32–43 hr after withdrawal.

Morphine Dose-Effect Curves

Figure 3A shows the effects of morphine on the motor activity of morphine dependent and nondependent animals during a 90-min experimental session. The lower doses of morphine, 0.1–3.0 mg/kg, produced a dose-related increase in the activity of both dependent and non-dependent rats. The higher doses of morphine, 10 and 30 mg/kg, decreased the activity of nondependent rats below levels obtained after the administration of saline. In contrast, these high doses of morphine still increased the activity of the dependent animals, although the dose-effect curve is clearly biphasic in this group, too.

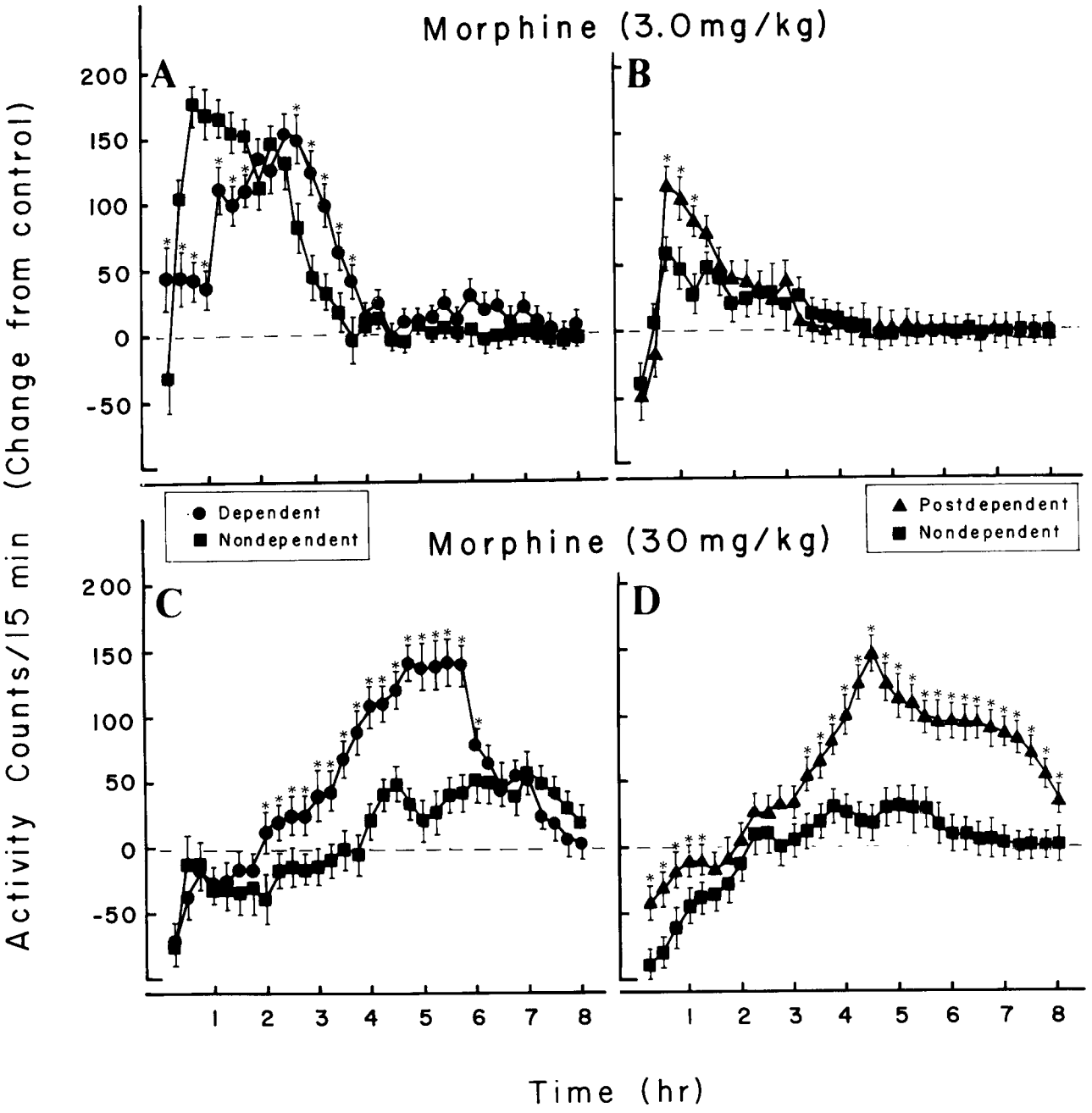

FIG. 4. The time course of the effects of a low (3.0 mg/kg) and a high dose (30 mg/kg) of morphine on the activity of nondependent and dependent rats, and six to ten weeks after morphine withdrawal, in the post-dependent and nondependent rats. The symbol (*) indicates a significant difference from the nondependent rats, $p<0.01$.

Six weeks after the withdrawal of morphine, the dose-effect curve for morphine was redetermined in the now post-dependent and nondependent animals (Fig. 3B). Morphine (0.1–3.0 mg/kg) produced a dose-related increase in the activity of both post-dependent and nondependent animals that was smaller in magnitude than that seen in these rats when they were first tested with morphine (Fig. 3A). Higher doses of morphine increased activity in the post-dependent rats to a greater extent than in the nondependent rats. The previously observed depressant effect of 30 mg/kg in the nondependent animals was not in evidence during retesting.

Saline and selected doses of morphine (1.0 and 10 mg/kg) were tested in nondependent rats that had scheduled access to water, in order to determine if the activity of rats that were housed individually and were given scheduled access to drinking solutions differed from the activity of rats that were housed two to a cage and allowed unrestricted access to water. There was no difference in the baseline activity or in

the effects of morphine on the activity of these animals compared to rats that were housed in group cages with continuous access to water.

Morphine Time-Effect Curves

Eight-hour time-effect curves for morphine (3.0 and 30 mg/kg) are compared in dependent and nondependent rats and six to ten weeks after morphine withdrawal, in the now post-dependent and non-dependent rats (Fig. 4). Morphine (3.0 mg/kg) produced an initial depression of activity in nondependent rats, followed by a stimulation that was equal in magnitude and duration to the activity seen in dependent rats (A). The time-effect curve in the dependent animals was shifted to the right and the peak stimulation occurred 1.5–2 hr later than in nondependent rats. Activity of both nondependent and dependent rats returned to baseline four hr after morphine administration. The post-dependent and nondependent animals were less sensitive to the stimulant effect of 3.0 mg/kg of morphine (B) than they were during the initial determination of the time-effect curve (A). Nevertheless, morphine produced a significantly greater increase in the activity of post-dependent rats than in the corresponding nondependent rats 30–75 min after injection.

The higher dose of morphine (30 mg/kg) produced an initial depression of activity followed by a delayed stimulation and return to baseline in nondependent rats during the eight-hr session (C). In contrast, the delayed increase in activity of the dependent animals occurred earlier and was significantly greater in both magnitude and duration than that observed in the nondependent animals. A more pronounced difference in the pattern of activity between groups was seen with the nondependent and post-dependent rats after the administration of 30 mg/kg of morphine (D). Post-dependent rats were relatively tolerant to the early depression of activity produced by morphine, and the delayed stimulation of activity remained significantly greater in magnitude and duration than that seen in the nondependent animals.

Naloxone Dose-Effect Curves

Naloxone did not alter the activity of non-dependent rats over a 1000-fold dose range (Fig. 5A). In contrast, 0.003 mg/kg of naloxone significantly increased the activity of dependent animals, while higher doses (0.3–3.0 mg/kg) produced a dramatic suppression of activity. In the post-dependent rats, all doses of naloxone produced a significant decrease in activity that was smaller in magnitude than that seen in dependent animals.

Weight loss has been associated with both abrupt and antagonist-precipitated withdrawal in dependent rats [1,10]. Therefore, we measured the change in body weight of the animals during testing in order to have an index of the severity of withdrawal induced by naloxone. Naloxone (0.003–3.0 mg/kg) did not alter the weight of nondependent or post-dependent animals during the 90-min experimental session (Fig. 5B). However, in dependent rats, naloxone produced a dose-related increase in weight loss that covaried with changes in motor activity.

Morphine Dose-Effect Curves in the Presence of Naloxone

Figure 6 shows the effects of morphine in combination with 0.3 mg/kg of naloxone on the motor activity of nondependent (A) and dependent (B) rats. Naloxone, alone, produced no effects on the activity of nondependent animals.

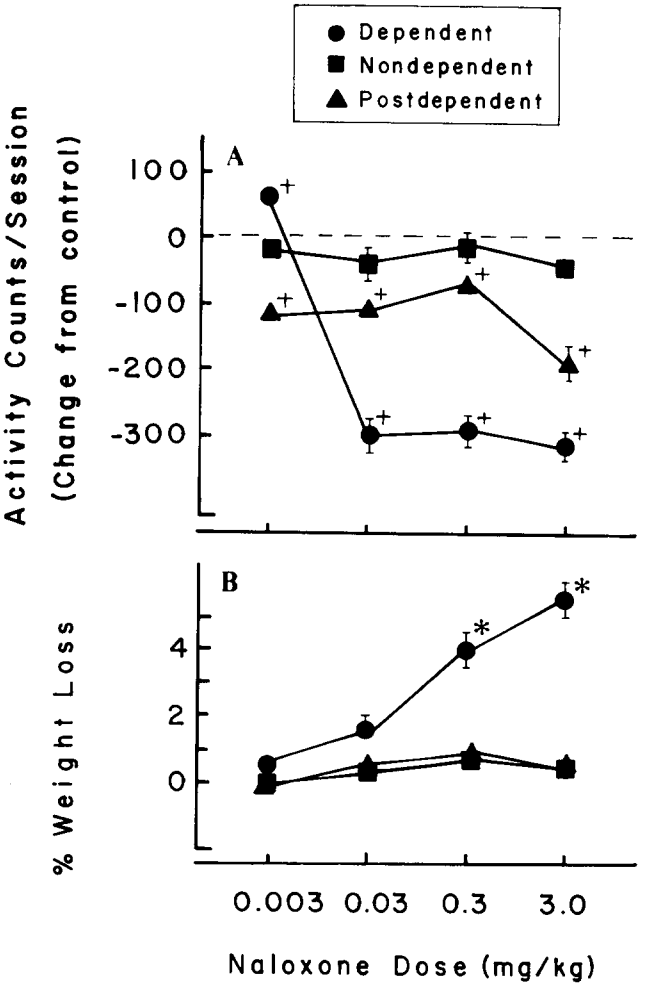

FIG. 5. The effects of naloxone on locomotor activity (A) and weight loss (B) in nondependent, dependent and post-dependent rats. The symbol (+) indicates a significant difference from baseline activity; the symbol (*) indicates a significant difference from the body weight of nondependent rats, $p<0.01$. Baseline activity counts in nondependent, dependent, and post-dependent rats are 289 ± 30, 736 ± 45 and 325 ± 33, respectively.

The concomitant administration of naloxone and morphine appeared to result in a shift to the right in the ascending limb of the morphine dose-effect curve of nondependent rats, with naloxone antagonizing the stimulation produced by low doses of morphine as well as the depression produced by high doses. In dependent rats, the morphine dose-effect curve was shifted downward and to the right when naloxone and morphine were administered together. The almost complete suppression of activity up to 10 mg/kg of morphine may be related to the precipitation of withdrawal by naloxone.

DISCUSSION

The dose- and time-effect curves for morphine in morphine-dependent and nondependent rats resembled the curves obtained by other investigators who used a variety of different techniques for measuring activity and for establishing morphine dependence [3, 6, 19, 21]. The dose-effect

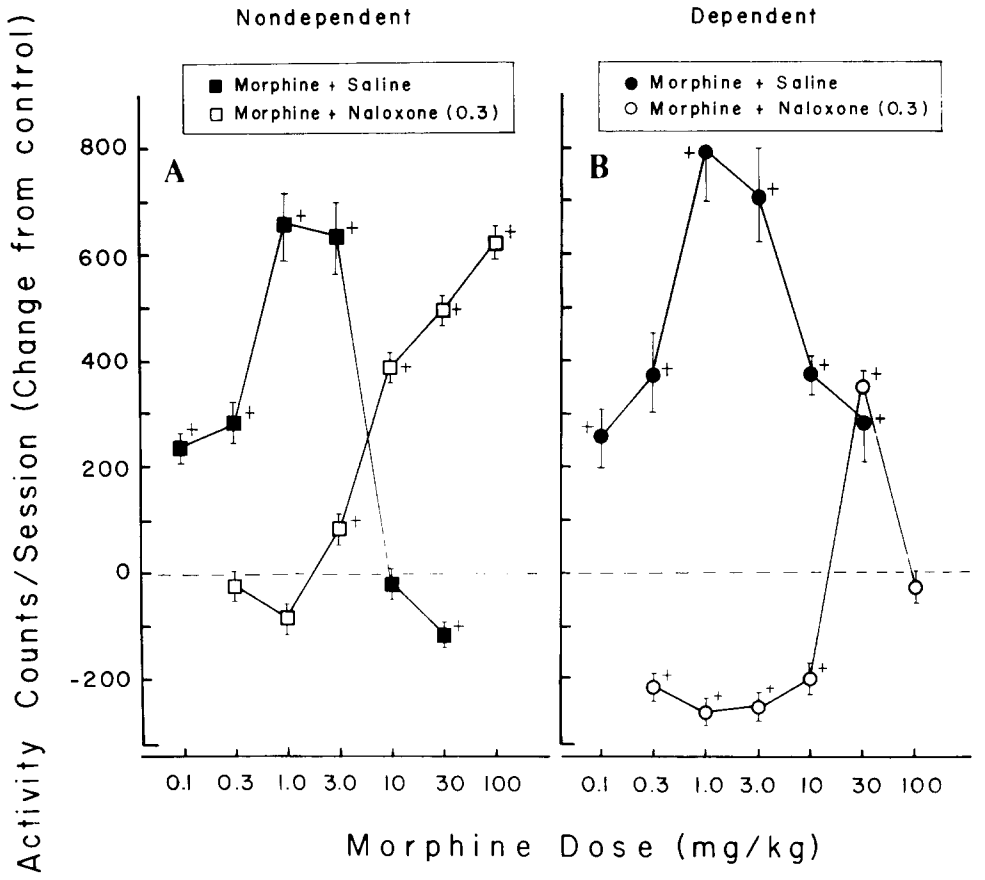

FIG. 6. The effects of morphine alone and in combination with 0.3 mg/kg of naloxone in nondependent (A) and dependent rats (B). Morphine dose-response curves are the same as those appearing in Fig. 3. The symbol (+) indicates a significant difference from baseline activity, $p<0.01$. Baseline activity counts are 235 ± 20 for nondependent rats and 675 ± 47 for dependent rats.

curves in both dependent and nondependent rats were biphasic, with activity being increased by the lower doses of morphine and reduced by the higher doses. Prominent tolerance developed to the depressant effect of the higher morphine doses in the dependent rats, but there was little evidence of tolerance to the stimulant effect of the low doses. In fact, the spontaneous activity of the dependent animals was more than twice that of the nondependent rats and remained elevated during twenty weeks of morphine access. The high spontaneous activity of the dependent rats, which presumably was due to the presence of morphine in the body, was comparable to the activity induced by 0.3–1.0 mg/kg of morphine in the nondependent animals. These results indicate that with a schedule of chronic oral morphine administration, tolerance to the depressant effect of morphine develops rapidly, while tolerance to the stimulant effect develops slowly, if at all. The depressant and stimulant effects were readily antagonized by naloxone, suggesting that both effects are mediated by opiate receptors. Similar differential development of tolerance to the depressant and stimulant effects of morphine has been reported for rats receiving multiple injections of morphine daily [21].

Seven weeks after morphine withdrawal, post-morphine-dependent rats were still tolerant to the depressant effect of high doses of morphine relative to the nondependent control group. These findings support and extend the results obtained in rats tested with a single, high dose of morphine three weeks to eight months after morphine withdrawal [4,18]. In addition, the delayed period of hyperactivity which follows the depression produced by high doses of morphine was still significantly enhanced in the post-dependent animals as compared to the nondependent rats.

Prior exposure of animals to morphine has resulted in long-lasting alterations in their responses to subsequent doses of the drug (e.g. [7]). In this study, we found protracted changes in sensitivity to the depressant action of morphine on locomotor activity. However, in a previous study, we found no protracted changes in the effects of morphine on schedule-controlled responding [5]. A possible explanation for this discrepancy is that the two behaviors involve different neuronal substrates that are affected differently by chronic morphine treatment. Moreover, the differential development of tolerance to the stimulant and depressant effects of morphine in dependent and post-dependent animals suggests that morphine-induced stimulation and depression of locomotor activity in the rat is mediated by different neuronal substrates.

Several difficulties arise concerning the interpretation of data in the morphine-treated and nondependent control animals in both stages of this study. The effects of morphine in the nondependent rats were different in the two determinations of the dose-effect curves. In the second stage of the

study, the nondependent animals were less sensitive to both the stimulant and depressant effects of morphine than they were during the initial determination of the dose-response curve, perhaps as a consequence of the development of tolerance from intermittent exposure to morphine during repeated testing [7]. However, tolerance to the stimulant effect of morphine on locomotor activity appears to develop only after prolonged exposure to high doses of the drug [21]. A more likely explanation appears to be age-related changes in sensitivity to morphine [20] due to the 27-week interval between the two determinations of the morphine dose-response curve and repeated exposure of the animals to the test procedure. An appropriate control for the post-morphine-dependent rats would be animals that were injected with saline and tested in the activity chambers twice a week during the 27-week period prior to determination of the morphine dose-response curve. However, maintenance of these saline-treated control rats matched for age and experimental experience is logistically difficult. Another possible problem involves the comparison of activity in animals housed under different conditions. We found no difference in the spontaneous activity of rats housed two per cage compared to that of rats housed individually and given scheduled access to water, probably because both groups were thoroughly habituated to the test procedure. The effects of selected doses of morphine in these two groups of rats were also similar. In the second stage of the study, post-dependent and nondependent animals were comparably housed and comparisons of the effects of morphine between these two groups of animals are not confounded by differences in age or housing conditions. Thus, it can be concluded that differences in the responses of post-dependent and nondependent rats to morphine during the redetermination of the dose-response curve are a direct consequence of the regimen of chronic morphine administration that only the former group received and is not due to differences in age or housing conditions.

The effects of abrupt withdrawal of morphine on the diurnal pattern of activity of dependent rats has not been clearly characterized. The data of several investigators [11, 13, 14, 16] have been confounded by the use of inappropriate controls and by recording activity at different time points following the last administration of morphine. In this study, activity was monitored for a 72-hr period beginning immediately after scheduled access to morphine. The elevated activity of the dependent animals during the first four hours, reflected the prominent stimulant action of morphine ingested prior to the beginning of the withdrawal session. Subsequently, activity of the dependent rats returned to the level of the nondependent control animals and remained low throughout the remaining light periods. The most striking alteration in activity of the dependent animals occurred during the dark periods: nondependent rats were very active, while the activity of the dependent rats remained relatively depressed. Suppression of activity during the second dark period correlated with the time-course of maximal body weight loss that occurred 24–48 hours after abrupt withdrawal of morphine in dependent rats given scheduled access to the drug [9].

Marked changes in activity have also been reported for dependent rats during the precipitation of withdrawal by narcotic antagonists [15,22]. Both sedation and hyperexcitability have been reported in dependent rats given equivalent doses of the narcotic antagonist, nalorphine [12, 13, 17]. These investigators characterized behavior on the basis of unquantified observations and based their findings on a single dose of nalorphine administered at different time intervals following the previous dose of morphine in these animals. In this study, naloxone did not alter the activity of nondependent rats over a 1000-fold range of doses. In contrast, the activity of dependent animals was significantly increased by a low dose of naloxone and almost completely suppressed by the higher doses. The depression of activity produced by high naloxone doses is generally consistent with the disruption of activity recorded during the 72 hours of abrupt withdrawal. These results indicate that the qualitative nature of the activity of dependent rats during precipitated withdrawal is dependent on the dose of narcotic antagonist administered.

Naloxone, itself, produced a decrease in the locomotor activity of post-dependent animals that was not dose-related. In a previous study, only a relatively high dose of naloxone, e.g. 5.0 mg/kg, decreased the activity of post-morphine-dependent rats [18]. The significance of the protracted change in sensitivity of post-dependent animals to naloxone remains to be determined.

REFERENCES

1. Akera, T. and T. M. Brody. The addiction cycle to narcotics in the rat and its relation to the catecholamines. *Biochem. Pharmac.* **17:** 675–688, 1968.
2. Ayhan, I. H. and A. Randrup. Behavioural and pharmacological studies on morphine-induced excitation of rats. Possible relation to brain catecholamines. *Psychopharmacologia* **29:** 317–328, 1973.
3. Babbini, M. and W. M. Davis. Time-dose relationships for locomotor activity effects of morphine after acute or repeated treatment. *Br. J. Pharmac.* **46:** 213–224, 1972.
4. Babbini, M., M. Gaiardi and M. Bartoletti. Persistence of chronic morphine effects upon activity in rats 8 months after ceasing the treatment. *Neuropharmacology* **14:** 611–614, 1975.
5. Brady, L. S. and S. G. Holtzman. Schedule-controlled behavior in the morphine-dependent and post-dependent rat. *Psychopharmacology* **70:** 11–18, 1980.
6. Buxbaum, D. M., G. G. Yarbrough and M. E. Carter. Biogenic amines and narcotic effects. I. Modification of morphine-induced analgesia and motor activity after alteration of cerebral amine levels. *J. Pharmac. exp. Ther.* **185:** 317–327, 1973.
7. Cochin, J. and C. Kornetsky. Development and loss of tolerance to morphine in the rat after single and multiple injections. *J. Pharmac. exp. Ther.* **145:** 1–10, 1964.
8. Domino, E. F., M. R. Vasko and A. E. Wilson. Mixed depressant and stimulant actions of morphine and their relationship to brain acetylcholine. *Life Sci.* **18:** 361–376, 1976.
9. Gellert, V. F. and S. G. Holtzman. Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. *J. Pharmac. exp. Ther.* **205:** 536–546, 1978.
10. Goode, P. G. An implanted reservoir of morphine solution for rapid induction of physical dependence in rats. *Br. J. Pharmac.* **41:** 558–566, 1971.
11. Gunne, L.-M. The excretion of noradrenaline and adrenaline in the urine of rats during chronic morphine administration and during abstinence. *Psychopharmacologia* **2:** 214–220, 1961.
12. Hanna, C. A demonstration of morphine tolerance and physical dependence in the rat. *Archs int. Pharmacodyn.* **124:** 326–329, 1960.

13. Kaymakcalan, S. and L. A. Woods. Nalorphine-induced "abstinence syndrome" in morphine-tolerant albino rats. *J. Pharmac. exp. Ther.* **117:** 112–116, 1956.
14. Kumar, R., E. Mitchell and I. P. Stolerman. Disturbed pattern of behaviour in morphine tolerant and abstinent rats. *Br. J. Pharmac.* **42:** 473–484, 1971.
15. Martin, W. R. Opioid antagonists. *Pharmac. Rev.* **19:** 464–521, 1967.
16. Martin, W. R., A. Wikler, C. G. Eades and F. T. Pescor. Tolerance to and physical dependence on morphine in rats. *Psychopharmacologia* **4:** 247–260, 1963.
17. Maynert, E. W. and G. I. Klingman. Tolerance to morphine. I. Effects on catecholamines in the brain and adrenal glands. *J. Pharmac. exp. Ther.* **135:** 285–295, 1962.
18. Nakamura, H., K. Ishii and M. Shimizu. Some altered responses in rats formerly dependent on morphine. *Psychopharmacology* **56:** 269–277, 1978.
19. Oka, T. and E. Hosoya. Effects of humoral modulators and naloxone on morphine-induced changes in the spontaneous locomotor activity of the rat. *Psychopharmacology* **47:** 243–248, 1976.
20. Saunders, D. R., R. M. Paolino, W. F. Bousquet and T. S. Miya. Age-related responsiveness of the rat to drugs affecting the central nervous system. *Proc. Soc. exp. Biol. Med.* **147:** 593–595, 1974.
21. Vasko, M. R. and E. F. Domino. Tolerance development to the biphasic effects of morphine on locomotor activity and brain acetylcholine in the rat. *J. Pharmac. exp. Ther.* **207:** 848–858, 1978.
22. Woods, L. A. The pharmacology of nalorphine (N-allylnormorphine). *Pharmac. Rev.* **8:** 175–198, 1956.