where the first summation was executed by series 557 in Jolley (10).

After differentiating Eq. A12 with respect to x and using summation formula 558 in Jolley (10), one obtains:

$$\left(\frac{\partial C^*}{\partial x}\right)_{x=l} = C_0^* \left\{\sqrt{\frac{\kappa}{D}}\frac{e^{-\kappa t}}{\sin l\sqrt{\kappa/D}} - \frac{1}{l} + \frac{2\kappa}{Dl}\sum_{n=1}^{\infty}\frac{(-1)^n e^{-(n\pi/l)^2 Dt}}{(n\pi/l)^2 - \kappa/D}\right\} \quad \text{(Eq. A13)}$$

Consequently, upon integration and simplifying by means of series 337 and 558 in Jolley (10), one obtains Eq. 8. Under experimental conditions, l, D, and κ will be rational numbers while π^2 is irrational so that $l^2\kappa/\pi^2 D \neq 1, 4, 9, 16, \ldots$. However, it may be sufficiently close to an integer to cause "round off" difficulties in computing the infinite sum.

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Acute Effects of Narcotic Analgesics on Behavioral Arousal in the Rat

W. MARVIN DAVIS▲ and CALVIN C. BRISTER*

Abstract □ Locomotor activity measured by photocell actometers was taken as an index of behavioral arousal in rats following acute administration of pentazocine, morphine, methadone, levorphanol, and meperidine. The intraperitoneal doses tested were 1.25, 2.5, 5.0, 10, and 20 mg./kg. The low doses of morphine and methadone and an intermediate dose of pentazocine produced an early (1st hr.) increase in motility. Higher doses of these three drugs and the lowest dose of levorphanol caused a delayed excitation (2nd–3rd hr.). An early inhibition of activity was seen for the higher doses of morphine, methadone, meperidine, and levorphanol but not for pentazocine. Meperidine did not elicit significant locomotor excitation in these doses. The enhanced motility after pentazocine and the narcotic analgesics was blocked by pretreatment with α-methyltyrosine.

Keyphrases □ Locomotor activity—effect of pentazocine and narcotic analgesics, compared to morphine, pretreatment with α-methyltyrosine, rats □ Pentazocine and narcotic analgesics—effect on locomotor activity, compared to morphine, pretreatment with α-methyltyrosine, rats □ Analgesics, narcotic (methadone, meperidine, levorphanol)—effect on locomotor activity, compared to morphine, pretreatment with α-methyltyrosine, rats □ Methadone—effect on locomotor activity, rats □ Meperidine—effect on locomotor activity, rats □ Levorphanol—effect on locomotor activity, rats □ α-Methyltyrosine pretreatment—effect of pentazocine and narcotic analgesics on locomotor activity, rats

Previous reports from this laboratory have analyzed the occurrence of locomotor stimulation following low doses of morphine in nontolerant rats (1–4). This effect had been little emphasized and had not been systematically evaluated in earlier works, which did, however, describe repeatedly an enhancement of motility by morphine occurring after an interval of repeated dosing in the study of tolerance and/or physical dependence (5–9). Certain studies have cited gross observations or limited data concerning such an effect in nontolerant rats (9–12). Locomotor excitation provides evidence for behavioral arousal in response to morphine in the nontolerant rat despite the classification of this species among those showing predominantly a response of depression and behavioral inhibition (13, 14).

Interest in this excitatory component of the CNS pharmacology of the opiates led to a consideration of the generality of the motility response seen with low doses of morphine. Specifically, it was of interest whether similar effects might be found not only after the synthetic narcotic analgesics but also after an agent of the narcotic antagonist–analgesic class. Therefore, methadone, meperidine, levorphanol, and penta-

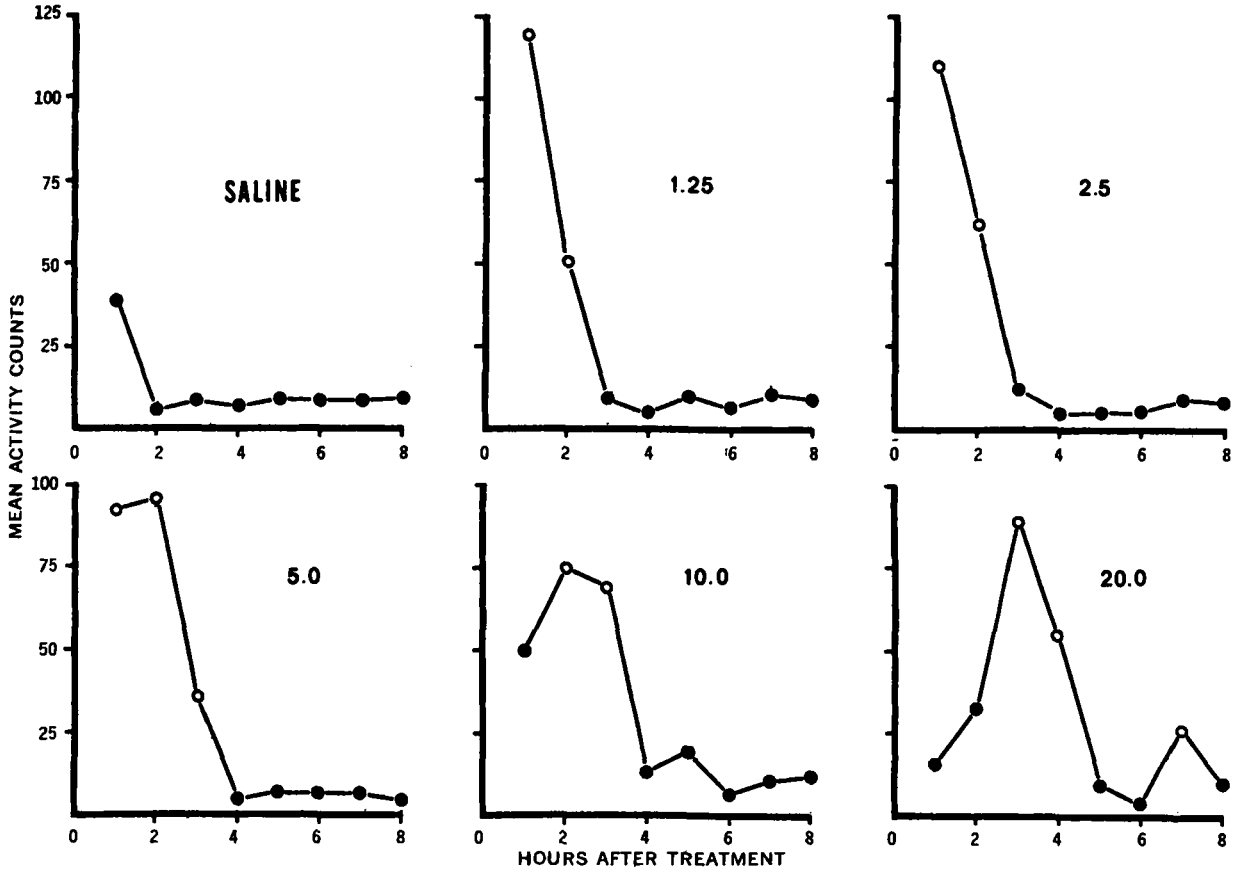

Figure 1—*Locomotor activity of rats following saline or several doses of morphine sulfate as indicated on the individual graphs (1.25–20.0 mg./kg.). Open circles represent hourly totals differing significantly from corresponding values of saline controls at* $p \leq 0.05$. *For each point,* $N = 18$.

zocine were examined to compare their actions to that of morphine. In addition to measuring the locomotor response to such agents alone, their interaction was tested with α-methyl-*p*-tyrosine, an agent that was previously found to be an effective inhibitor of the motor excitatory response to morphine in nontolerant rats (3, 4).

EXPERIMENTAL

Experimental subjects were male Wistar rats[1], which were assigned randomly on receipt to treatment groups and housed three per cage in metal cages (41 × 24.5 × 18 cm.) with food and water available *ad libitum*. They were placed in a room with an altered light cycle of 4:00 p.m. to 4:00 a.m., and 7–9 days was allowed for adaptation to the environmental conditions. Most rats attained a desired weight range of 225–235 g. by the time the locomotor activity study was begun. Each rat received only one dose of only one drug.

The photocell actometer units used (15) consisted of a circular alley, 7.6 cm. wide and 15 cm. high, with an external diameter of 37.5 cm. The inner wall held a container for food and a water bottle. Photocells of this apparatus cannot be deactivated several times in succession. An adjacent photocell must be subsequently deactivated to reset the first one, so that only large horizontal movements may be recorded. The actometers were located in a windowless, sound-shielded room, which also contained a masking white-noise generator to attenuate further any outside sounds. The temperature was generally maintained at 24 ± 1°.

Experiments began 1.5–2 hr. after light onset. On the 1st day, all rats were injected with saline, placed in actometer units individually, and allowed 24 hr. for adaptation to the actometer. On the 2nd day, they were injected with saline or with the test drug. Beginning immediately following injection, motility data were recorded hourly for 8 hr. Statistical analyses tested for differences between the saline control and each treatment group at each hourly observation period by means of one-way analysis of variance and Duncan's multiple range test (16).

The locomotor activity responses to several dosages of morphine and its surrogates were evaluated first. With the exception of methadone, all drugs were tested at the same five levels: 1.25, 2.5, 5.0, 10, and 20 mg./kg. For methadone the highest dosage was reduced to 16 mg./kg. because of toxicity. Each of the six treatment groups was composed of 18 subjects. During every actometer session (a 48-hr. period), three rats were tested from each treatment group.

Subsequent experiments tested for a relationship between central adrenergic function and the excitation produced by morphine and certain surrogates by determining the effect of α-methyltyrosine pretreatment on drug-induced motility. For this purpose, a dose of each analgesic agent was chosen that had produced the greatest activity response at the 1st hr. after treatment. For comparison, the effect of α-methyltyrosine on the activity evoked by 1.0 mg./kg. dextroamphetamine also was tested. These studies utilized four treatment groups: saline–saline, α-methyltyrosine–saline, saline–drug, and α-methyltyrosine–drug. On the 2nd day of the experimental session, saline or α-methyltyrosine pretreatment was administered 3.5–4 hr. prior to the injection of the test drug or saline. For the interaction study with dextroamphetamine, α-methyltyrosine was administered in a dose of 50 mg./kg. However, in experiments with analgesics, 100 mg./kg. was used.

A total recording period of only 4 hr. was utilized for the interaction studies because earlier data showed that the maximum activity produced by the selected dosages occurred within the first 3 hr. postinjection. Analysis of variance was applied to the cumulative motility counts over the first 3 hr. and separately for the 2nd and 3rd hr., but only the former values are reported here.

For each individual experiment, a solution or suspension of the drugs to be used was freshly prepared. Saline (0.9%) was used to

[1] National Laboratory Animal Co., Creve Coeur, Mo.

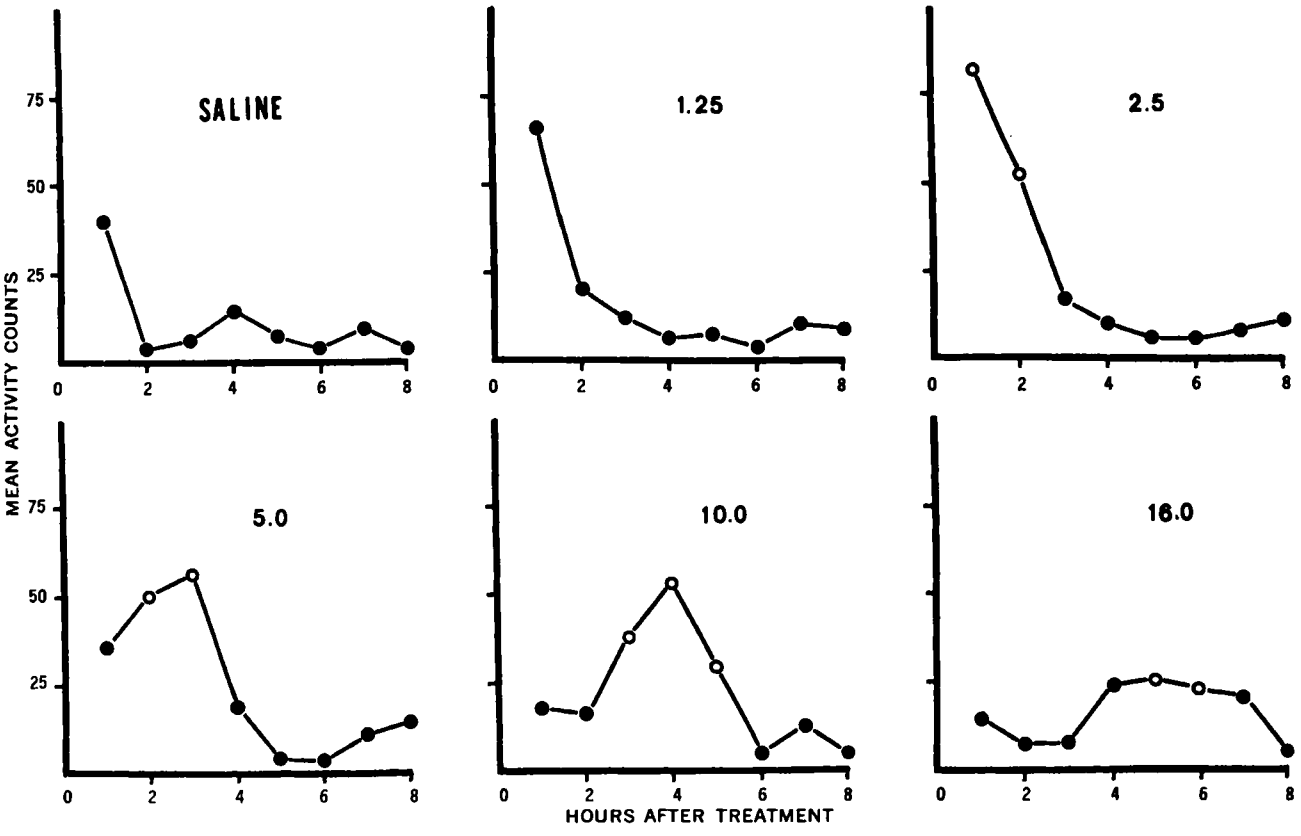

Figure 2—*Locomotor activity of rats following saline or several doses of methadone hydrochloride as indicated on the individual graphs (1.25–16.0 mg./kg.). Open circles represent hourly totals differing significantly from corresponding values of saline controls at* $p \leq 0.05$. *For each point,* $N = 18$.

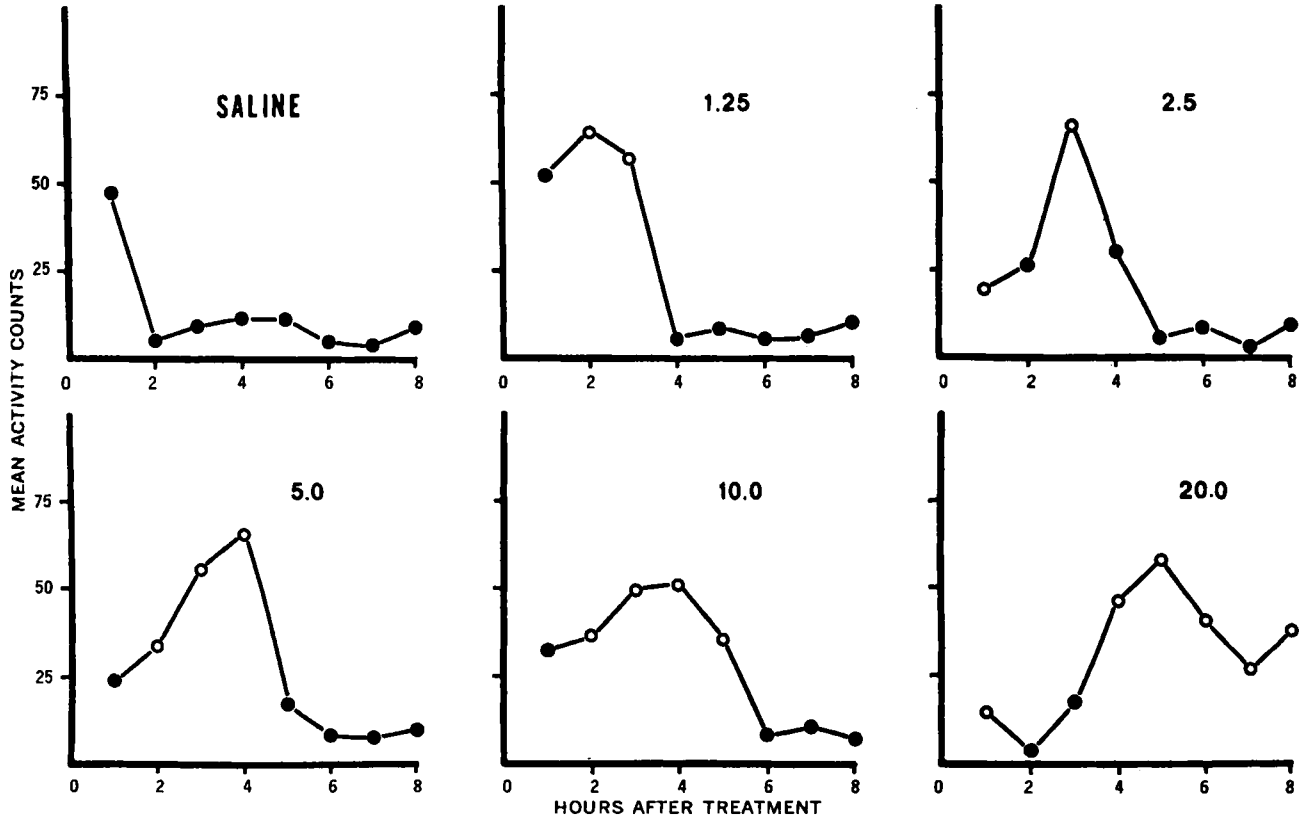

Figure 3—*Locomotor activity of rats following saline or several doses of levorphanol tartrate as indicated on the individual graphs (1.25–20.0 mg./kg.). Open circles represent hourly totals differing significantly from corresponding values of saline control at* $p \leq 0.05$. *For each point,* $N = 18$.

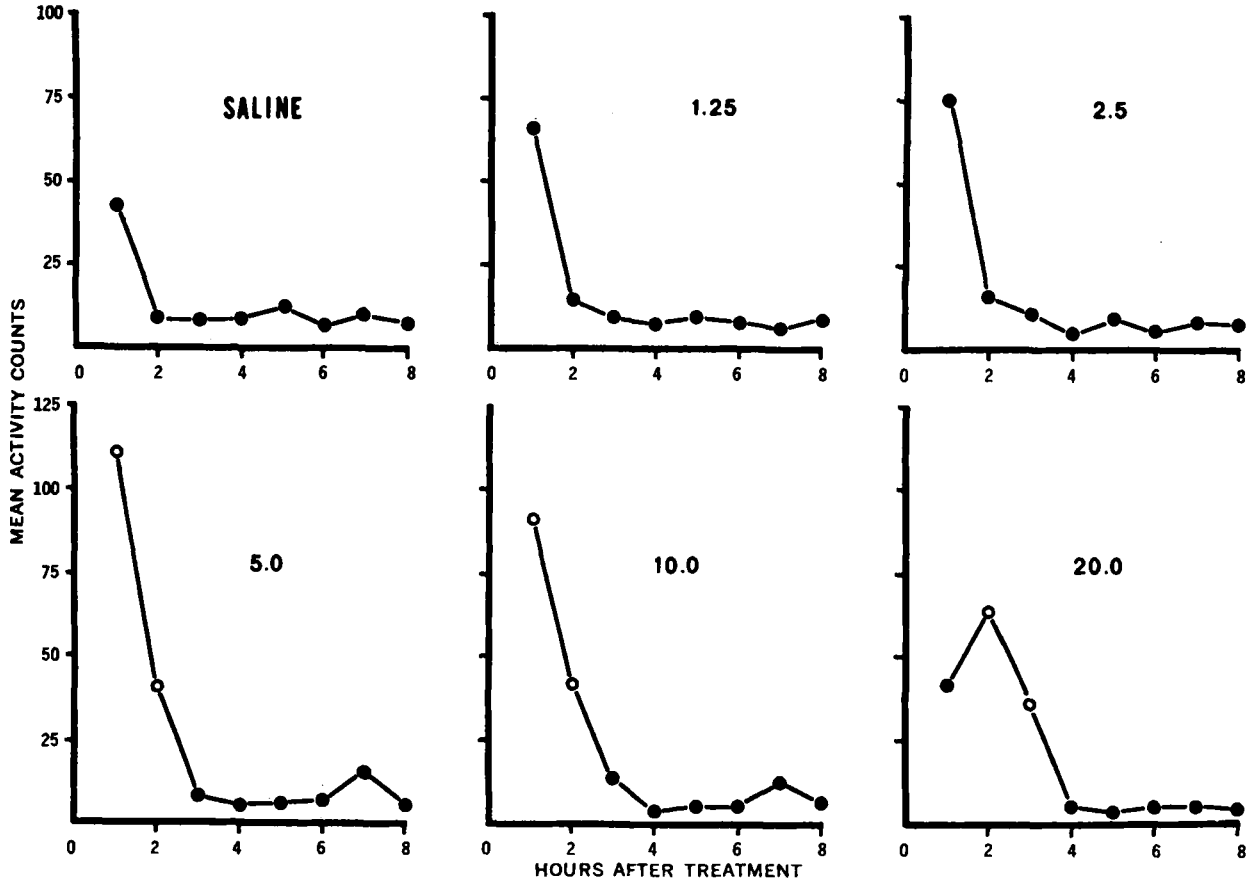

Figure 4—*Locomotor activity of rats following saline or several doses of pentazocine lactate as indicated on the individual graphs (1.25–20.0 mg./kg.). Open circles represent hourly totals differing significantly from corresponding values of saline controls at* $p \leq 0.05$. *For each point,* $N = 18$.

prepare solutions of morphine sulfate, levorphanol tartrate, and dextroamphetamine sulfate and a suspension of D,L-α-methyl-*p*-tyrosine[1]. Solutions of methadone hydrochloride, meperidine hydrochloride, and pentazocine lactate were prepared by dilution of commercial injectable solutions with saline. All drugs were administered in a volume of 1.0 ml./kg. As a control for each drug, an equal volume of 0.9% saline was injected. All injections were by the intraperitoneal route. Dosages given are in terms of the salts used.

RESULTS

Dose–Response Relationships for Analgesics on Locomotor Activity—Graphical presentations of results are given in Figs. 1–5. Saline-treated control rats characteristically displayed a moderate level of activity during the 1st hr., which is attributable to a combined effect of handling and injection procedures and of the behavioral arousal evoked by being removed from and returned to the actometer. Activity fell greatly in the 2nd hr. and remained low throughout the remaining 6 hr. of recording, except for a slight rise often found between the 3rd and 6th hr.

The activity patterns over time for several dosage levels of morphine are shown in Fig. 1. These are in close agreement with previous results from this laboratory (1, 2). The three lower doses produced a high initial excitatory response. For the lower two the peak activity was at the 1st hr., with significant activity continuing only during the 2nd hr. With the 5.0-mg./kg. dose, the peak was observed at the 2nd hr., and the duration was greater since a lower but still significant activity was evident at the 3rd hr. A further delay in peak activity was produced by increasing the dosage to 10 and 20 mg./kg. The former dose had no significant effect at the 1st hr. but caused peak activity at the 2nd hr., which was maintained with only slight reduction through the 3rd hr. The response to 20 mg./kg. suggested a biphasic effect: initial depression followed by excitation. A biphasic pattern has been more clearly demonstrated in other observations for which the 24-hr. adaptation was omitted so that activity at the 1st hr. was elevated. Peak excitation occurred at the 3rd hr., and high activity continued through the 4th hr.

The activity patterns for all of the other analgesics except meperidine showed a general similarity to that of morphine. The only apparent differences were in the level of peak activity achieved, in the duration of either depressant or stimulatory phase, and in the dosage producing a particular response pattern.

Methadone never showed as high a peak excitation as morphine (Fig. 2). The response to a 2.5-mg./kg. dose was like that of morphine at 1.25 or 2.5 mg./kg., while the response to 5.0 mg./kg. resembled morphine at 10 mg./kg. The response to methadone at 10 mg./kg. matched that with 20 mg./kg. morphine, and at 16 mg./kg. it was comparable to activity found in another study (2) for 40 mg./kg. morphine.

Levorphanol in doses of 1.25 and 2.5 mg./kg. (Fig. 3) produced responses closely resembling those after 10 and 20 mg./kg. of morphine, respectively. There was a suggestion of a biphasic response after levorphanol doses of 2.5, 5.0, and 10 mg./kg., while 20 mg./kg. clearly caused initial depression followed by excitation. No dose caused as high a degree of excitation as did morphine. There was a delay in time of peak excitatory response and an increased duration of excitation as the levorphanol dose was increased from 1.25 to 20 mg./kg.

Pentazocine at 1.25 and 2.5 mg./kg. had no significant effects (Fig. 4). However, the time-activity curves after 5.0 and 10 mg./kg. were very similar to those of morphine at 1.25 and 2.5 mg./kg., respectively. The pattern of activity following 20 mg./kg. pentazocine was comparable to that of 10 mg./kg. morphine.

Results with meperidine were not comparable to morphine at any dose tested (Fig. 5). Only 10 mg./kg. gave a small but significant increase in activity at the 2nd hr. The 20-mg./kg. dose showed a significant 1st hr. depressant effect along with a small but significant increase in activity at the 3rd hr.

[1] Regis Chemical Co., Chicago, Ill.

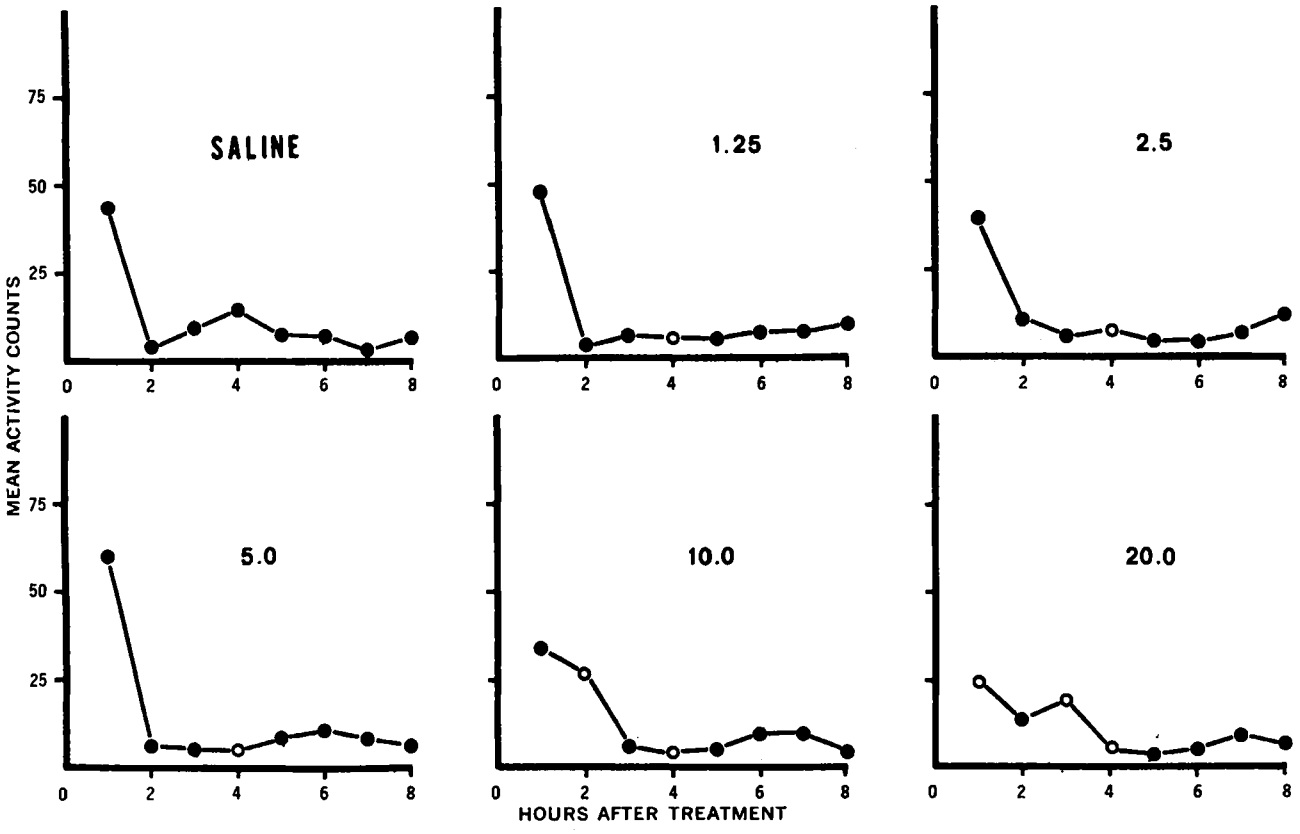

Figure 5—*Locomotor activity of rats following saline or several doses of meperidine hydrochloride as indicated on the individual graphs (1.25–20.0 mg./kg.). Open circles represent hourly totals differing significantly from corresponding values of saline controls at* $p \leq 0.05$. *For each point,* $N = 18$.

Thus, these results indicate that characteristic dose–activity patterns observed with morphine were matched by methadone at about one-half, by levorphanol at about one-tenth, and by pentazocine at 2–4 times the morphine dosage. On the other hand, meperidine failed to show clearly any pattern corresponding to those found with morphine.

Effect of α-Methyltyrosine on Locomotor Activity—The inhibition by α-methyltyrosine of the initial excitatory response to dextroamphetamine and to selected dosages of the analgesics (except for meperidine) is shown in Fig. 6. Statistical comparisons between means for total activity over the first 3 hr. after drug showed that in all cases α-methyltyrosine blocked the drug-induced excitatory response; *i.e.*, the activity of the combination did not differ from the saline controls or α-methyltyrosine–saline groups. Although the 3-hr. means for the α-methyltyrosine control groups were, in most instances, somewhat lower than saline controls, the differences were nonsignificant, and the apparent deficit in activity occurred mainly during the 1st hr.

DISCUSSION

While morphine in low doses (1, 2) has been known to stimulate motility of nontolerant rats, reports of such an effect have been lacking for the synthetic analgesics (methadone, levorphanol, and meperidine), although all have shown such activity in mice (17). One previous report of increased motility in the rat after a narcotic antagonist analgesic appeared recently for pentazocine (18). This work showed that α-methyltyrosine pretreatment blocked the motility response to pentazocine, another result that is confirmed by the present study. In addition, the morphine data of this study, both alone and in combination with α-methyltyrosine, provide confirmation for earlier findings (3, 4) in a different strain of rat.

The activity response to methadone and levorphanol was qualitatively similar to that after morphine, although of lesser magnitude. With both drugs the rats displayed a progressive delay in onset of peak activity with increasing dosage, as has been found characteristic of morphine (2). Pentazocine caused a maximum activation comparable in magnitude to that of morphine, but the shift over time with increasing dosage was less clearly evident in this dosage range. Meperidine in the doses reported here caused no consistent elevation of activity over controls. However, a later supplementary study with a dose of 30 mg./kg. gave a result very similar to that shown here for 20 mg./kg. of levorphanol (Fig. 3), having a quite delayed onset and peak of activity. Even with this observation, the pattern of response to meperidine in rats clearly differed from that of the other analgesics.

It has been postulated that locomotor excitatory effects of morphine are elicited through an action at a receptor site which is separate from and more sensitive than the one that causes locomotor inhibitory effects (2). The similarity in response patterns between morphine and the analgesics tested here (except meperidine) would allow the extension of this concept to these morphine surrogates. Such quantitative differences as were found could be attributed largely to differences in rates of metabolic inactivation. In view of these results in rats, it is interesting to note that meperidine in mice also caused the least increase in motor activity among several narcotic analgesics including morphine, methadone, and levorphanol (17). A difference in relative affinities for excitatory and inhibitory receptor sites could possibly explain the differing response pattern of meperidine compared to the other narcotic analgesics.

While a 50-mg./kg. dose of α-methyltyrosine blocked most of the motility response to dextroamphetamine, a dose of 100 mg./kg. was required to block completely the response to the four analgesics. The latter dose was the same that Holtzman and Jewett (18) found effective against the motility effects of pentazocine. The failure of morphine, methadone, levorphanol, and pentazocine to produce locomotor excitation after α-methyltyrosine suggests the dependence of their stimulatory effects upon a release of brain catecholamines. The same supposition was made earlier for morphine on the basis of a lowering of brain catecholamine levels during its action (9, 14, 17) as well as the interaction of morphine and α-methyltyrosine (4). In the case of pentazocine, this supposition also was put forth recently on the basis of both types of data (18). However, differences were observed in brain amine effects and

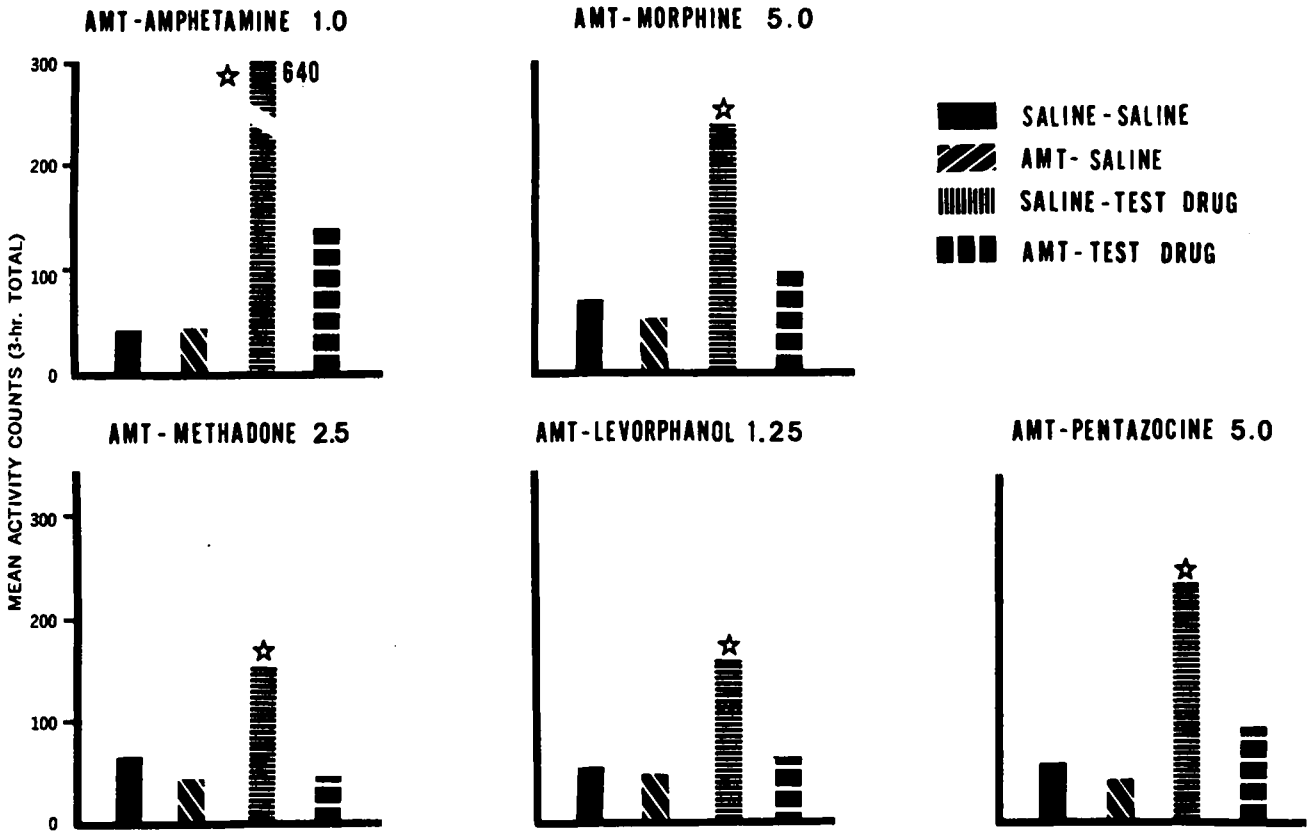

Figure 6—*Effect of α-methyltyrosine (I, AMT) on drug-induced locomotor activity of rats. Saline or I was injected intraperitoneally 3.5–4 hr. before each test drug. Dosages of drugs tested were dextroamphetamine, 1.0 mg./kg.; morphine sulfate, 5.0 mg./kg.; methadone hydrochloride, 2.5 mg./kg.; levorphanol, 1.25 mg./kg.; and pentazocine lactate, 5.0 mg./kg. Values indicated by stars were the only ones differing significantly* ($p \leq 0.05$) *among the respective treatment groups. For each group,* $N = 18$.

interactions with naloxone, which were taken to suggest that some agonist actions of pentazocine are mediated by receptors distinct from those on which morphine acts (18). The present data do not provide a basis for speculation on that point but do indicate some qualitative similarity in the responses to the agonist actions of morphine and pentazocine in terms of a locomotor activity measure.

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