Open access • Journal Article • DOI:10.1007/BF00402708

Effects of morphine on behavior maintained by four simple food-reinforcement schedules — Source link

Travis Thompson, J. Trombley, D. Luke, D. Lott

Institutions: University of Minnesota

Published on: 01 Jan 1970 - Psychopharmacology (Springer-Verlag)

Reports from the Research Laboratories

of the

Department of Psychiatry

University of Minnesota

Effects of Morphine on Behavior Maintained by Four Simple Food Reinforcement Schedules

by

T. Thompson, J. Trombley, D. Luke and D. Lott

Report Number PR-69-5

September 5, 1969

Effects of Morphine on Behavior Maintained by Four Simple Food Reinforcement Schedules[1]

T. Thompson, J. Trombley, D. Luke and D. Lott

September 5, 1969

PR-69-5

Department of Psychiatry

University of Minnesota

[1]This research was supported in part by U.S.P.H.S. Research Grant MH-15349 to the University of Minnesota.

Though morphine is considered primarily an analgesic, it has substantial behavior effects as well (Kreuger, Eddy, and Sumwalt, 1941; Wikler, 1950). Most investigations of morphine's behavioral actions have revealed behavioral depression (e.g., increased latencies, increased running time, decreased rate of lever pressing), though some studies have reported behavioral stimulation as well (Djahanguiri, Richelle and Fontaine, 1966; McMillan and Morse, 1967; Tsou, 1963; Woods, 1969). Whether a drug produces behavioral depression or stimulation depends on numerous factors, with drug dose and current maintaining contingencies being among the most important variables (Thompson and Schuster, 1968).

Many reports of morphine's behavioral effects have employed one dose, or if more than one dose, only a single value of relevant behavioral variables (e.g., a single value of the reinforcement schedule). It is becoming increasingly clear, studies using a single parameter value of behavioral variables, like single dose studies, render questionable an interpretation of the behavioral changes produced by the drug (Dews and Morse, 1961; Kelleher and Morse, 1969).

The purpose of the present study was to determine the effects of 1.0, 3.0 and 6.0 mg/kg intraperitoneally morphine sulfate, on a lever pressing operant maintained by three values each of four simple food reinforcement schedules in rats. Data concerning the influence of type of schedule, schedule value and drug dose were ascertained from the results of this investigation.

METHOD

Subjects: Twelve experimentally naive Sprague-Dawley male albino rats, weighing from 240-350 grams, and ranging from 100 to 120 days of age at the beginning of the experiment, served as subjects.

Apparatus: Three Gerbrands Rat Operant Test Chambers, Model A equipped with microswitch levers, motor-type feeders for 45 mg Noyes food pellets, house lights and ventillating fans were used. Each chamber was enclosed in a sound-attenuating compartment and was connected via cables to electromechanical control and recording equipment in an adjacent room. All data were recorded on digital counters (accuracy 10 counts per second) and Gerbrands cumulative recorders.

Procedure: Subjects were individually housed in nearby animal quarters, with a 12 hour light-12 hour dark cycle, and constant room temperature of 70°F. Food (Purina rat chow) and water were freely available for the first two weeks in the laboratory. During the succeeding two weeks the daily food ration was reduced until body weight reached 80% of the free-feeding weight. Conditioning began with two one-hour magazine training sessions during which such subjects were conditioned to approach the food magazine and eat pellets when presented at variable intervals, with a mean of one minute. Subsequently, a continuous reinforcement schedule was in effect until each subject's performance stabilized. One of four types of simple reinforcement schedules were then instated:

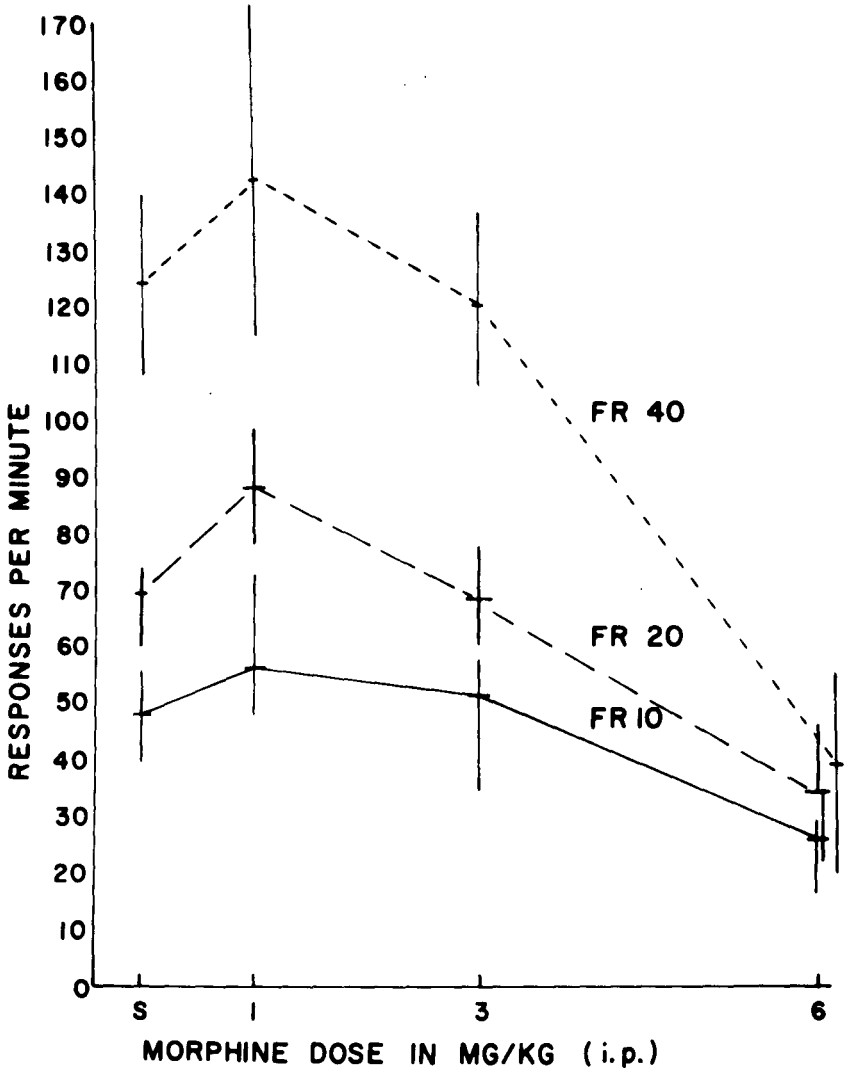
Fixed Interval (FI), Variable Interval (VI), Fixed Ratio (FR), and Variable Ratio (VR) (Ferster and Skinner, 1957). The schedule values were: FI 15 secs., FI 30 secs., and FI 120 secs.; VI 15 secs., VI 30 secs., and VI 120 secs.; FR 10, FR 20, and FR 40, VR 10, VR 20, and VR 40. In FI schedules, reinforcement was forthcoming on the first response after a fixed period since the last reinforcement (e.g., 15 sec on an FI 15 sec schedule) while in VI schedules, reinforcement was forthcoming following varying periods of time since the last reinforcement with a specified mean interval (e.g., a mean of 15 sec on a VI 15 sec schedule). Similarly, while reinforcement was presented following a fixed number of responses on FR schedule (e.g., 10 responses on an FR 10 schedule), reinforcement was presented following varying numbers of responses on VR schedule, with a mean number of responses remaining the same for a given schedule value (e.g., a mean of 10 responses on a VR 10 schedule).

Three rats were conditioned on each of the four types of schedules (FI, VI, FR, and VR). Each rat was tested at three values of the type of schedule on which it was conditioned (e.g., FI 15, FI 30, FI 120 seconds) at each drug dose (1.0, 3.0 and 6.0 mg/kg). Following stabilization on continuous reinforcement, the schedule was changed to the smallest value of the type of schedule on which the subject was to be conditioned. Conditioning was continued until day-to-day overall rate changes for each subject were less than plus or minus one-tenth of the mean response rate of the preceding three days. Morphine or saline solutions were administered intraperitoneally, immediately before placing the animals in the test chamber for one-hour daily test sessions. Morphine sulfate

was dissolved in saline at concentrations of 1.5 mg/cc, and sterile isotonic saline was used on control days. Saline was administered for two days, followed by one of the three morphine sulfate doses. The order of morphine dosing was balanced within each group so one subject received the lowest dose first, another the intermediate dose first, and the third the highest dose first, etc. Two saline days succeeded between each morphine day, until all three morphine doses had been tested once at a given reinforcement schedule value. Then, the value of the schedule was increased to the next highest value (e.g., from FR 10 to FR 20) and conditioning without injection resumed. The same criterion of stability at the second schedule value was used, before drug administration was reinstated. Once again, the order of morphine doses was balanced for the three subjects and two saline days were interspersed between the drug days. The same procedure was subsequently replicated for the highest schedule value. That is, each subject received a total of nine doses of morphine, one each, at each of three values of a single type of reinforcement schedule. Overall response rates and cumulative records of lever pressing were recorded.

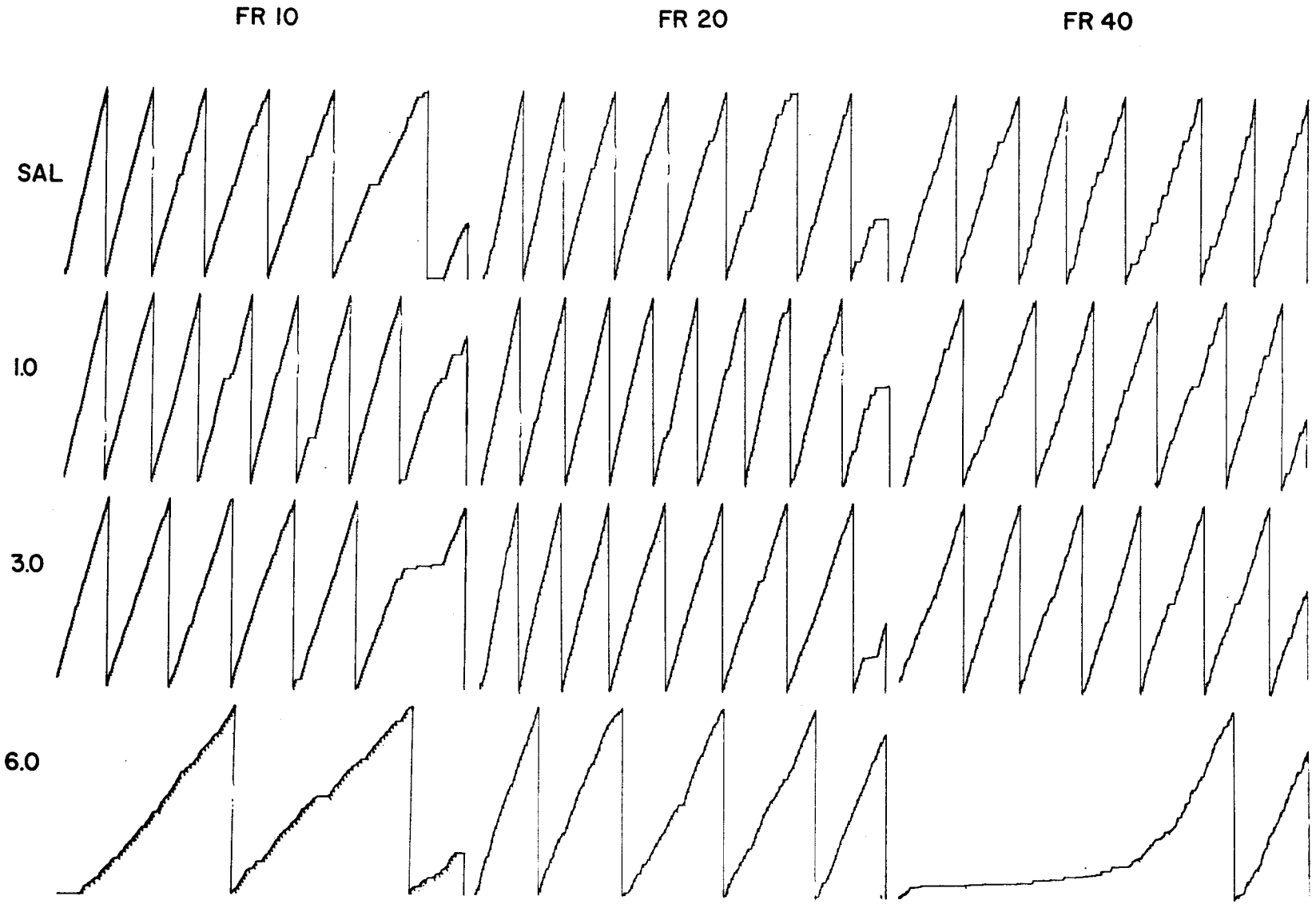
RESULTS

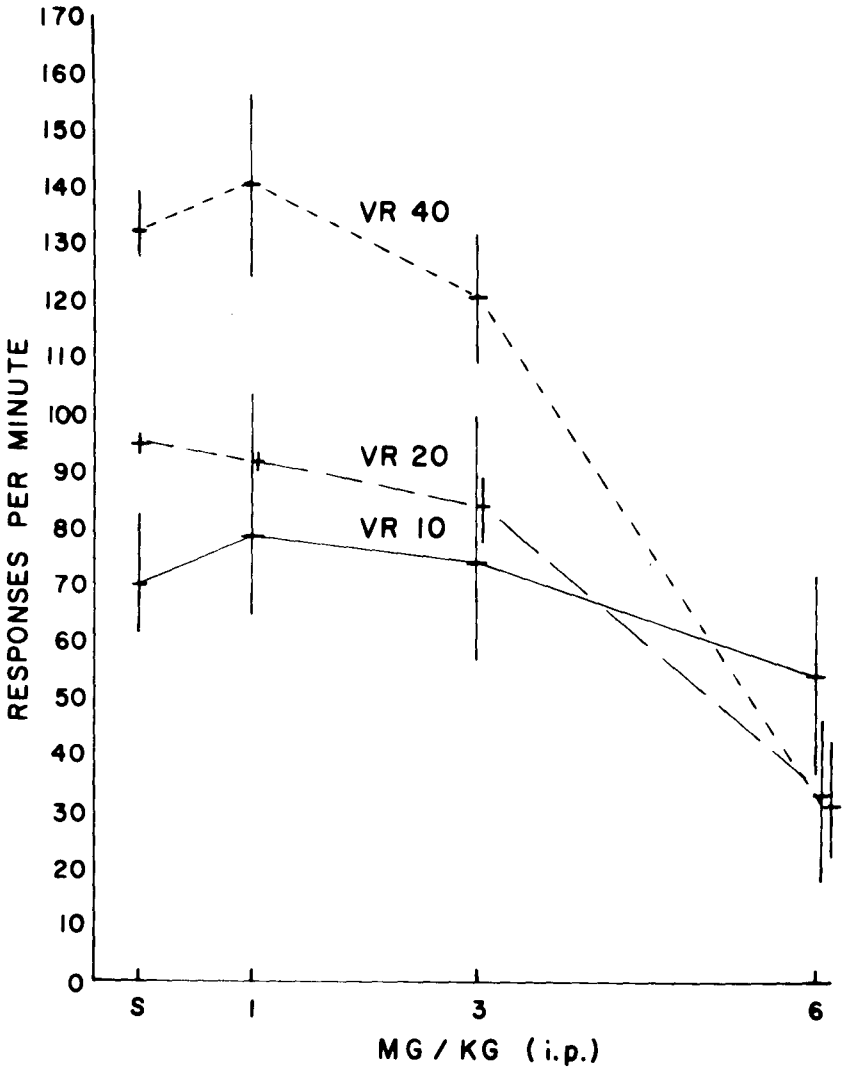
Fixed Ratio: Figure 1 shows the mean responses per minute for subjects maintained on FR 10, FR 20, and FR 40 schedules, following administration of 1.0, 3.0, and 6.0 mg/kg of morphine sulfate, and saline. A Friedman two way analysis of variance by ranks, reveals a significant difference

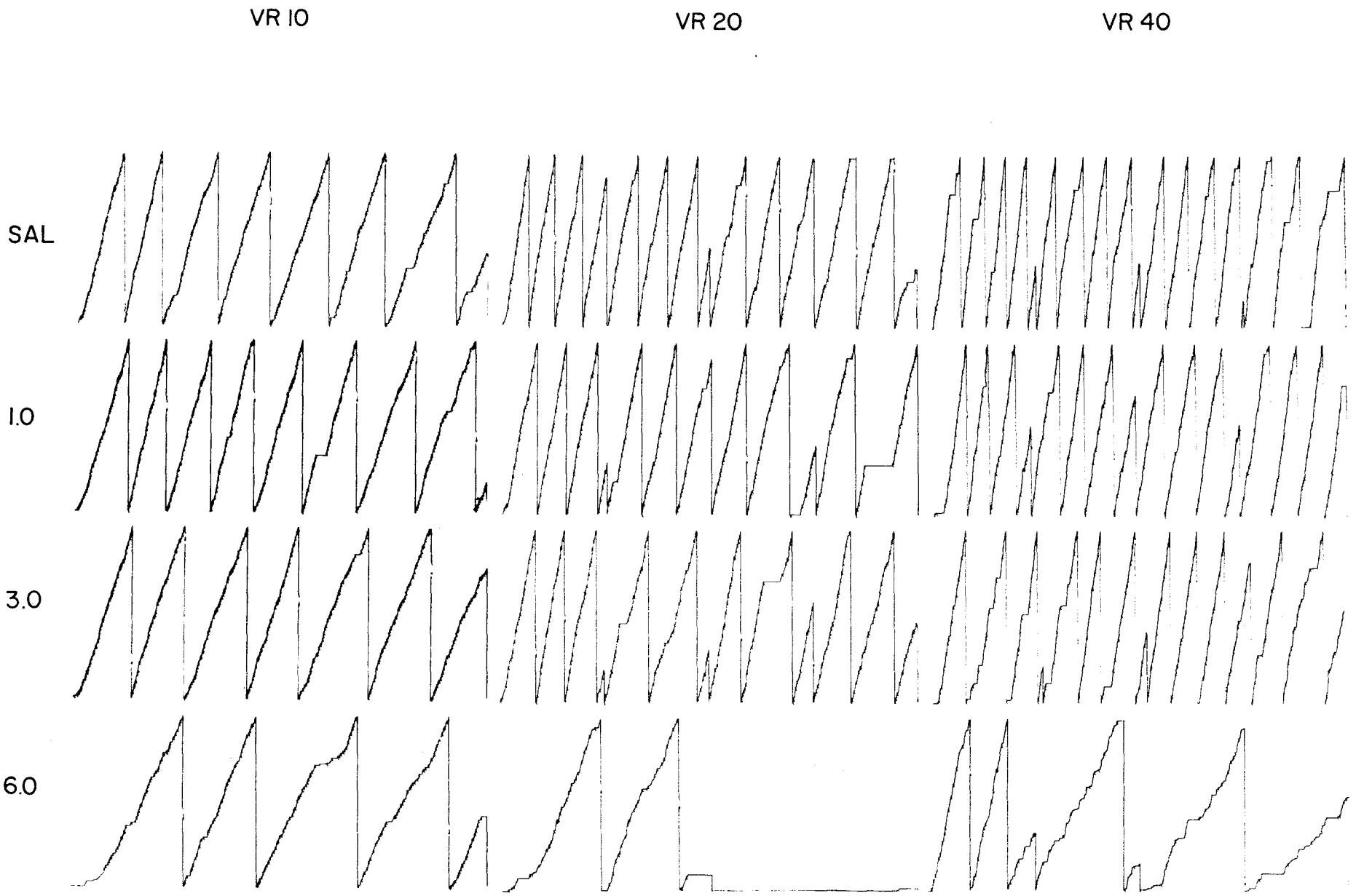

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
RESPONSES PER MINUTE
FR 40
FR 20
FR 10
S
1
3
6
MORPHINE DOSE IN MG/KG (i.p.)

among response rates due to morphine dose ($X^2 = 25.4$, $p < .001$), and schedule value ($X^2 = 8.0$, $p < .02$). The mean rates were higher at every schedule value when animals received 1.0 mg/kg than saline, while the mean rates at 6.0 mg/kg were below control values. Figure 2 shows cumulative records of lever pressing at each schedule value and dose of morphine tested, as well as sample saline records. Examination of the records for subjects treated with 1.0 mg/kg, particularly the FR 40 performance, reveals that the length of the post-reinforcement pauses were generally shorter, yielding a higher overall rate. At 3.0 mg/kg performance at FR 20 and FR 40 schedule values revealed reduced running rates, and at 6.0 mg/kg, all schedule values maintained intermediate running rates with substantial pausing at the high schedule value (FR 40).

Variable Ratio: Figure 3 presents the mean overall response rates for subjects treated with 1.0, 3.0, and 6.0 mg/kg of morphine sulfate, and saline maintained on VR 10, VR 20, and VR 40 schedules. Friedman two way analysis of variance by ranks reveals that response rates differ significantly due to morphine dose ($X^2 = 17.9$, $p < .001$) and schedule value ($X^2 = 6.0$, $p < .05$). As with FR performance, rates were higher at 1.0 mg/kg (except for VR 20), and lower at 6.0 mg/kg. The rate-increasing effect is particularly noticeable when 1.0 mg/kg is administered to subjects maintained on a VR 10 schedule (Figure 4). The effect appears to be due to reduction of pausing rather than increased running rate. As the size of the mean ratio increases, pausing increases, and the amount of pausing is proportional to morphine dose. Unlike FR performance, there is no indication of intermediate rates below 6.0 mg/kg. At


FR 10
FR 20
FR 40
SAL
1.0
3.0
6.0

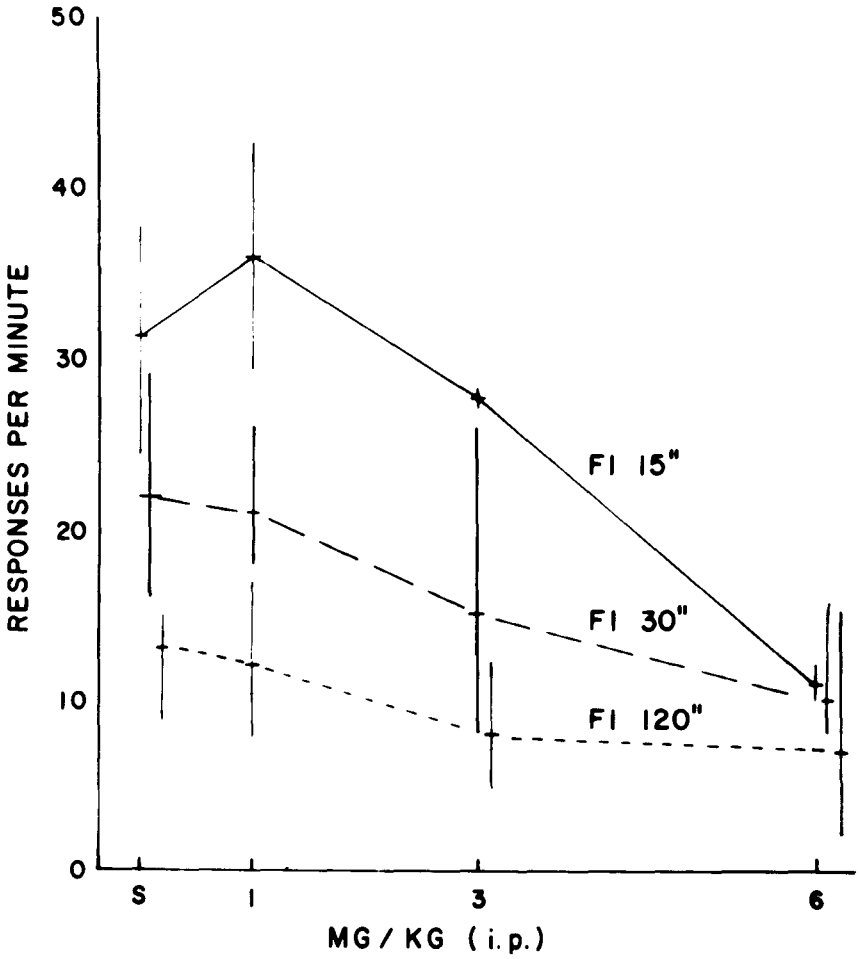

RESPONSES PER MINUTE
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
VR 40
VR 20
VR 10
S
1
3
6
MG / KG (i.p.)

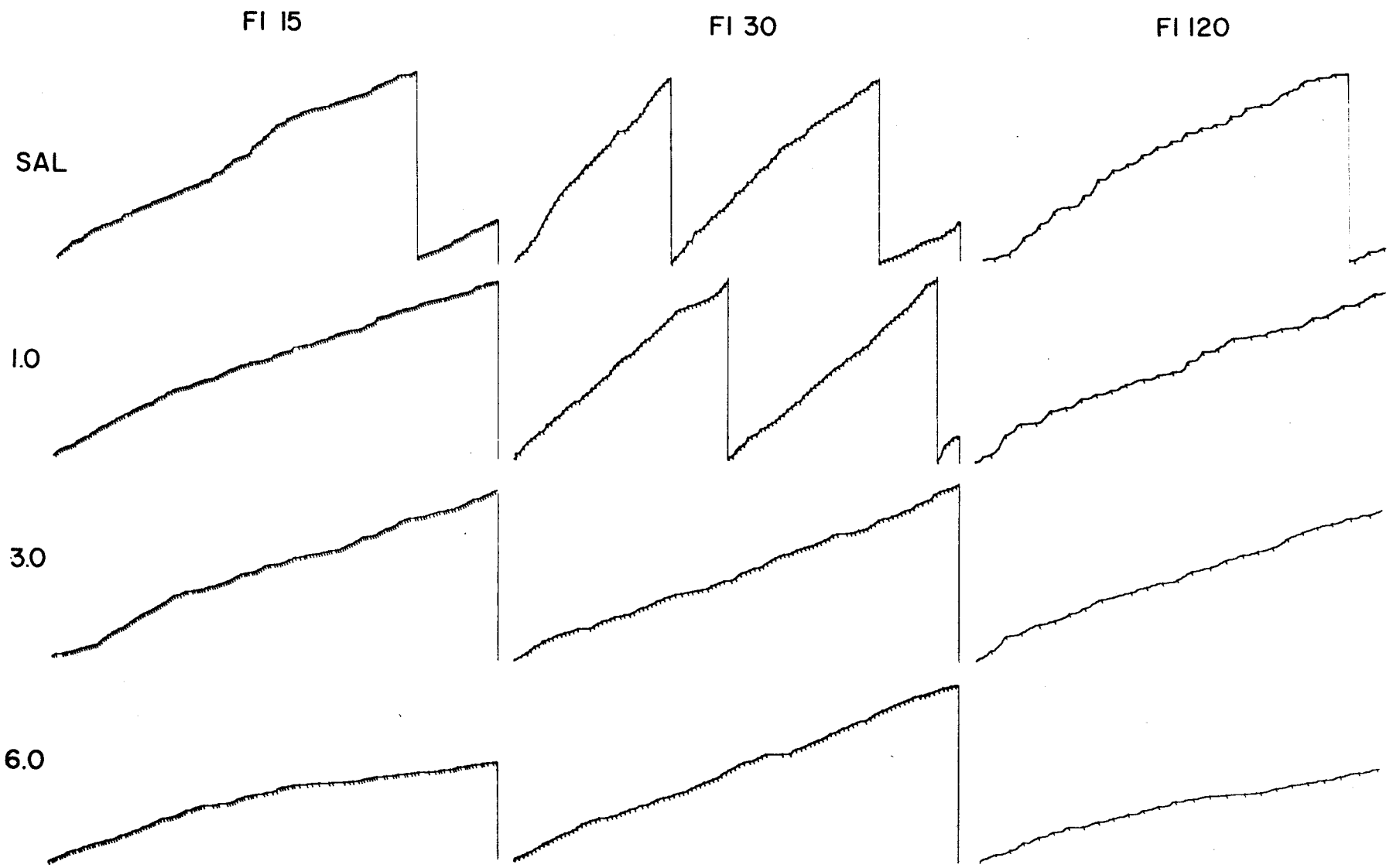

VR 10
VR 20
VR 40
SAL
1.0
3.0
6.0

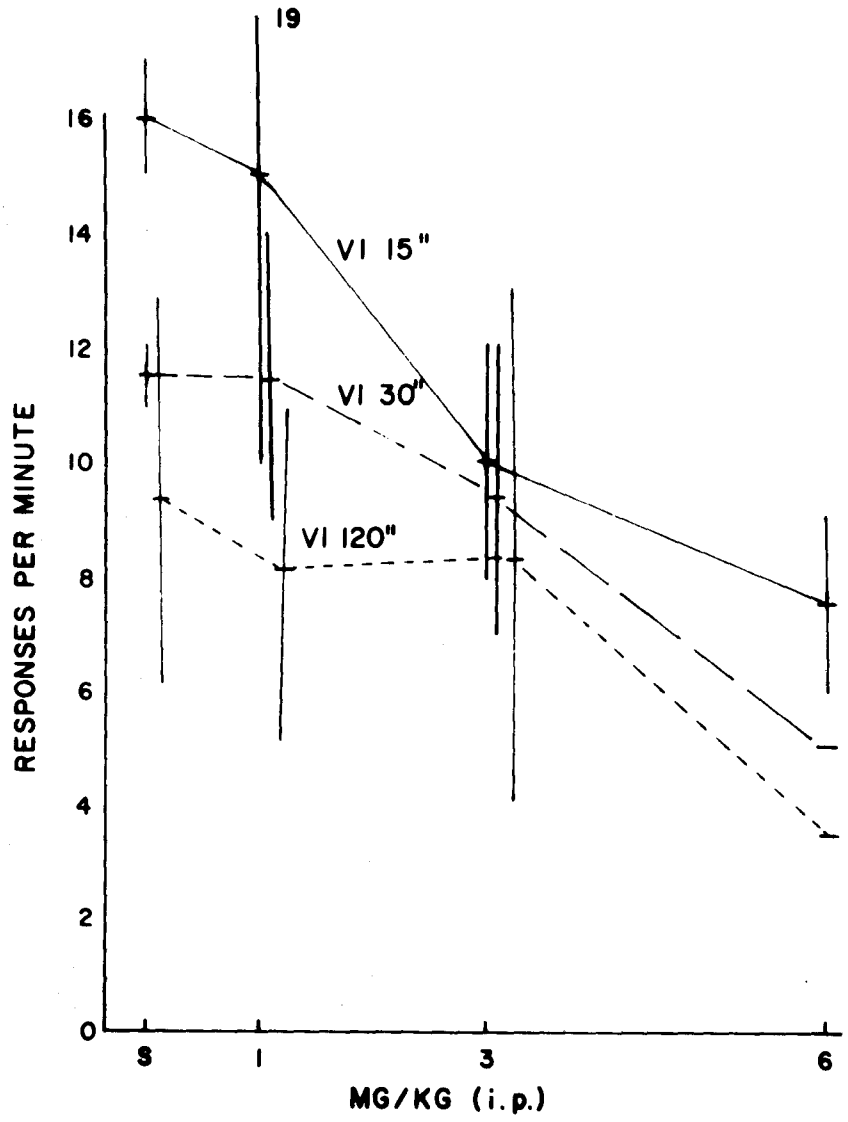
6.0 mg/kg there are both intermediate rates with coarse grain, and extensive pausing.

Fixed Interval: The mean responses per minute for subjects maintained on FI 15, FI 30, and FI 120 second schedules, treated with 1.0, 3.0, and 6.0 mg/kg of morphine sulfate and saline, are shown in Figure 5. While the mean response rate for subjects maintained on a FI 15 sec schedule, administered 1.0 mg/kg of morphine is higher than the saline control, all morphine doses produced reductions in mean response rate at all other schedule values. A Friedman two way analysis of variance by ranks reveals that response rates differ significantly due to morphine dose ($X^2 = 25.0$, $p < .001$) and schedule value ($X^2 = 12.5$, $p < .01$). Careful examination of the cumulative records (Figure 6) reveals that the rate increase at 1.0 mg/kg at FI 15 seconds is due to increased terminal response rates during the fixed intervals. At other doses and schedule values, morphine reduced terminal rates below their saline counterparts. At FI 120, morphine also slightly increased rates during the early portion of each interval, though the reduction of terminal rates was sufficiently greater to produce an overall rate decrement.

Variable Interval: Figure 7 presents the mean responses per minute for subjects maintained on VI 15, VI 30, and VI 120 second schedules, treated with saline 1.0, 3.0, and 6.0 mg/kg of morphine sulfate. In every case response rates at 3.0 and 6.0 mg/kg were lower than saline controls, and at VI 15 and VI 120, response rates were lower at 1.0 mg/kg and equal to saline controls at VI 30 sec. Response rates differ significantly due to morphine dose ($X^2 = 25.4$, $p < .001$) and schedule value ($X^2 = 8.2$,


50
40
30
20
10
0
RESPONSES PER MINUTE
FI 15"
FI 30"
FI 120"
S
1
3
6
MG / KG (i.p.)

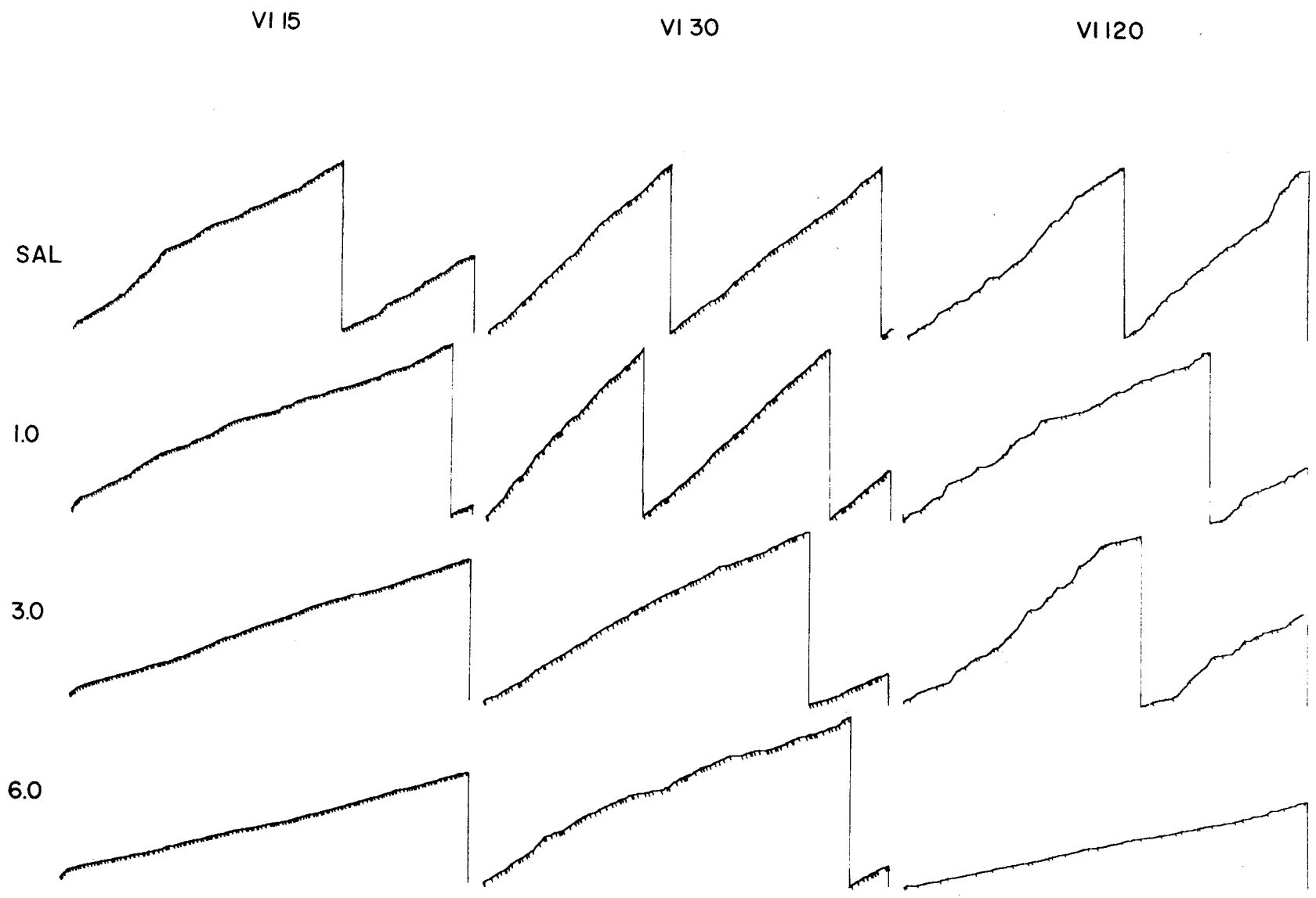

FI 15
FI 30
FI 120
SAL
1.0
3.0
6.0

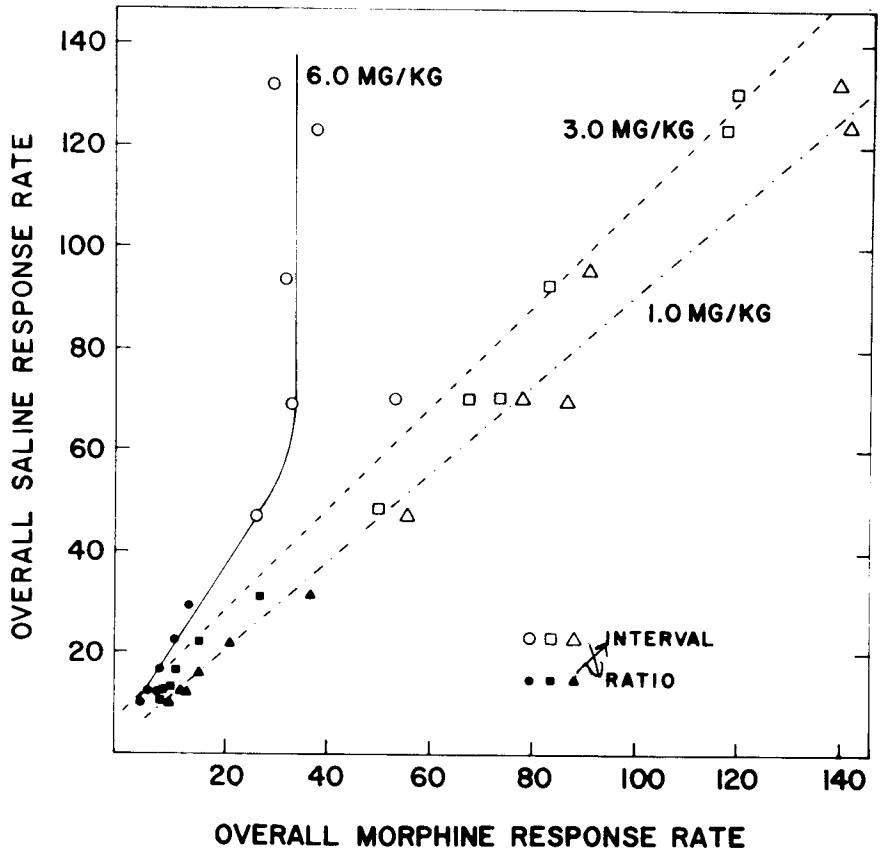

19
16
14
12
10
8
6
4
2
0
RESPONSES PER MINUTE
VI 15"
VI 30"
VI 120"
S
1
3
6
MG/KG (i.p.)

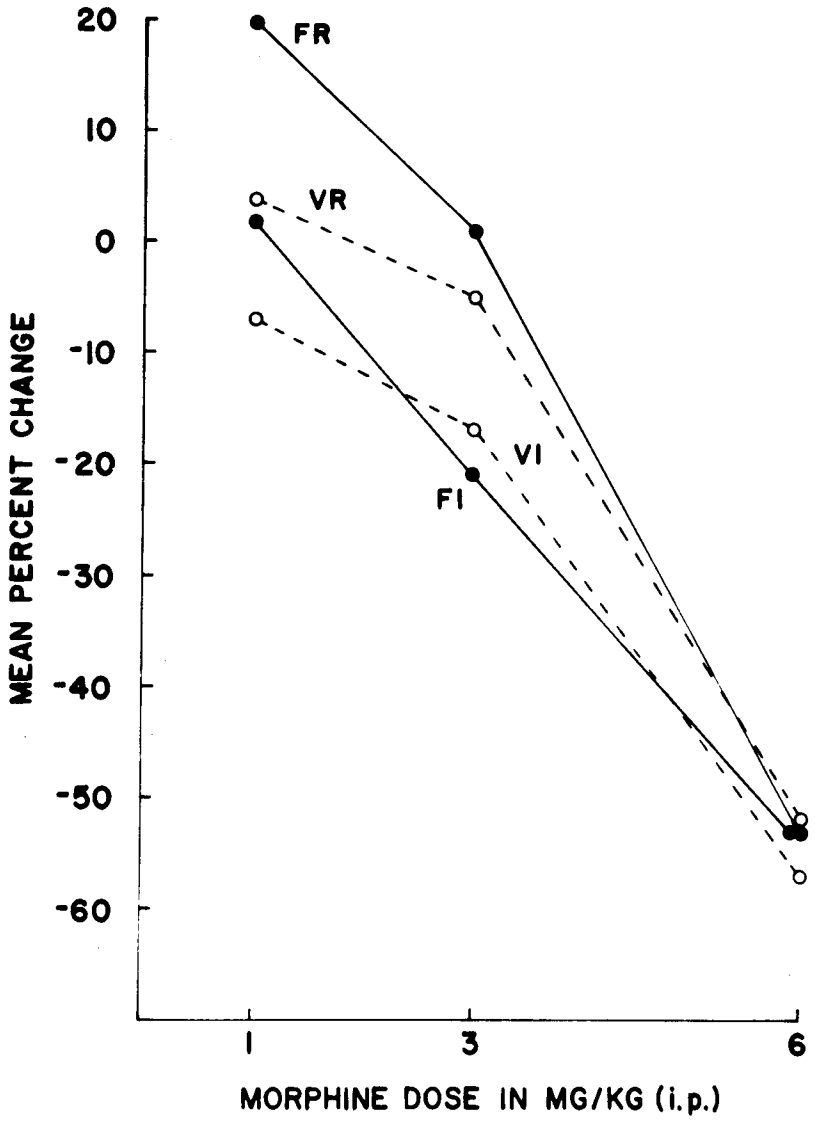
$p < .02$), using a Friedman two way analysis of variance by ranks. Figure 8 reveals no systematic effects on performance within reinforcement cycles due to morphine at VI 15 and VI 30 seconds while at VI 20 seconds, morphine appears to accentuate intermediate and low rates between reinforcements, which is apparent in saline treated subjects, as well.

The degree to which the effect of morphine on overall rate varies with the baseline saline response rate is shown in figure 9. The points for the ratio and interval schedules form a continuous line for each dose, with ratio points comprising the top six values on each line (open figures) and interval schedules comprising the bottom six points (closed figure). There was a positive rectilinear relation between baseline saline rate and morphine rates for 1.0 and 3.0 mg/kg doses of morphine, with the slopes varying with dose ($Y = 2.05 + .88X$, at 1.0 mg/kg and $Y = 3193 + 1.05X$ at 3.0 mg/kg, calculated using the method of averages) (Guilford, 1954). At 6.0 mg/kg the relation between saline and morphine rates was curvilinear, and is displayed by the freehand curve shown in figure 9. For the 1.0 and 3.0 mg/kg doses, the morphine response rate varied directly with the rate under saline conditions. At 6.0 mg/kg, low morphine response rates varied with baseline saline rate, but at baseline rates above 60 responses per minute, morphine rate did not vary with saline rate.

Figure 10 shows the data in which the three values of each schedule have been summed and expressed as mean percent change at each morphine dose. At 1.0 and 3.0 mg/kg doses, the ordinal relations among the four


VI 15
VI 30
VI 120
SAL
1.0
3.0
6.0


140
120
100
80
60
40
20
6.0 MG/KG
3.0 MG/KG
1.0 MG/KG
INTERVAL
RATIO
OVERALL SALINE RESPONSE RATE
20
40
60
80
100
120
140
OVERALL MORPHINE RESPONSE RATE


20
10
0
-10
-20
-30
-40
-50
-60
MEAN PERCENT CHANGE
FR
VR
VI
FI
1
3
6
MORPHINE DOSE IN MG/KG (i.p.)

schedules in terms of the percent change produced by morphine is consistent for 8 of the 9 values, with the FR and VR curves lying above the FI and VI curves. At 3.0 mg/kg, the VI and FI points are inverted. The values for all schedules converge at from 52 to 56% rate change at 6.0 mg/kg. Thus, while figure 9 indicated the effects of morphine on overall response rate depend on baseline rate generated by a schedule, figure 10 reveals that the relative rate change also varies with type of schedule.

DISCUSSION

The effects of morphine on operant lever pressing maintained on four simple food reinforcement schedules varies with the type of schedule, the schedule value and morphine dose. At low doses (1.0 mg/kg) rate-increase was observed on ratio schedules, while in most cases rate diminution was produced by the same dose using interval schedules. Thus, behavioral "stimulation" depends on dose, schedule, and schedule value. Response rate reductions were obtained with all schedules at all values using a 6.0 mg/kg dose, suggesting that behavioral "depression" is less dependent on schedule and schedule value. However, the relative degree of rate reduction using ratio schedules was greater for larger schedule values at a given dose than at smaller schedule values, and conversely the relative rate reduction in interval schedules is greatest at short interval values.

The rate-increasing effects on ratio schedules produced by low morphine doses appears to be due to reduced pausing, which is particularly noticeable with FR schedules. Rate reducing effects at 3.0 and 6.0 mg/kg doses were first associated with intermediate running rates, and later with

extensive pausing, particularly at larger schedule values. Of the six interval schedule values used, a rate-increasing effect was only observed at FI 15. Examination of cumulative records revealed this increased rate was due to higher terminal rate during each of the fixed intervals. The rate-reducing effects of morphine at all other interval schedule values and doses was associated with reduction of the terminal rate of fixed interval performance, and overall rate reduction in VI performance. At VI 120 seconds, substantial rate reductions were also seen between reinforcements at 1.0 and 3.0 mg/kg, accentuating an effect already evident in saline control performance.

The acute behavioral effects of morphine on operant performance have received relatively little systematic experimental attention. Hill, Pescor, Belleville and Wikler (1957) found that 9 mg/kg subcutaneously administered to rats trained on a continuous food reinforcement schedule, decreased lever pressing rate by approximately 80% one hour after administration. Using an FI 3 schedule, Weiss (1956) reported 1.6 mg/kg s.c., produced little or no effect on the overall rate of the food--reinforced operant. Djahnguiri, Richelle and Fontaine, 1966) chronically administered 0.2 mg/kg of morphine to cats conditioned on an FI 2 minute schedule of milk reinforcement. The drug produced little initial effect, however after repeated administrations, the overall rate increased. Shifts in relative frequency distributions of responses over successive portions of the fixed interval revealed that the rate increase was due to increased responses occurring toward the end of the intervals.

Tsou (1963), using a multiple FI FR schedule found that morphine decreased pausing early in the FI component, and caused overall rate decrements at higher doses in both components. McMillan and Morse (1967) reported that 1.0 mg/kg intramuscularly of morphine, increased the rate of key pecking for food reinforcement by pigeons in the FI component of a multiple FR 30 FI 5 minute schedule. In the same dose, morphine had no effect on the response rate during the FR component. Unlike Djahnguiri, Richelle and Fontaine (1966), McMillan and Morse found that the proportion of responses occurring during the early portion of the fixed interval component increased following morphine administration. The rate-increasing effects of low doses of morphine on the FI component performance of a multiple FI FR schedule was confirmed by Woods (1969), in monkeys and pigeons.

With the exception of Tsou's (1963) study, all of the above reports have been limited to single schedule values, and include only FI and FR schedules. Rate increases have not previously been reported using ratio schedules, though in the present study, both FR and VR rates were increased at the 1.0 mg/kg dose at all schedule values. These data also conflict with previous reports in that, morphine produced a rate-increase at only one value of FI schedule, at one dose, whereas other investigators have reported rate-increases on FI schedules across a broader range of conditions. The reasons for these discrepancies cannot be determined from these data. Several obvious differences among studies, such as the type of subjects, schedule values, and the fact that most other studies reporting rate increases in FI schedules, used multiple FI FR schedules, might account for

the observed differences between our results and those previously reported. The only other studies using simple FI schedules (Djahnguiri, Richelle and Fontaine, 1966) reported a rate increase, on repeated administration of a low dose 0.2 mg/kg in cats, or no significant change in response rate by rats administered 1.6 mg/kg s.c. (Weiss, 1956).

Increasing evidence indicates the effects of drugs on schedule-maintained performance can depend, to a considerable degree, on the response rates prior to drug administration (Dews, 1958). In the present study, overall saline rate was related to rate at 1.0 and 3.0 mg/kg morphine doses. At the 6.0 mg/kg dose, baseline rate varied with morphine rate only at low baseline rates. These data are consistent with Dews' (1958) hypothesis that a drug's behavioral effects can be determined by the response rate generated by a given schedule. The fact that the points for a given morphine dose fell on the same curves regardless of schedule (figure 9), is the most convincing evidence supporting the rate-dependency hypothesis.

However, when the data were expressed as percent change from the baseline saline rate (i.e., when baseline rate differences were controlled), the four schedules generated different curves at 1.0 and 3.0 mg/kg doses (figure 10). Thus, not only the overall response rates generated by schedules were important, but some more specific schedule-effect was involved. In all likelihood, overall rate interacts with subtler patterns of inter-response times generated by reinforcement schedules to determine a drug effect.

REFERENCES

Dews, P.B. Analysis of effects of pharmacological agents in behavioral terms. Fed. Proc., 1958, 17, 1024-1030.

Dews, P.B. and Morse, W.H. Behavioral pharmacology. Ann. Rev. Pharmacol., 1961, 1, 145-174.

Djahanguiri, B., Richelle, M., and Fontaine, O. Behavioral effects of a prolonged treatment with small dose of morphine in cats. Psychopharmacologia, 1966, 9, 303-372.

Guilford, J.P. Psychometric Methods, 2nd ed. New York: McGraw-Hill, 1954.

Hill, H.E., Pescor, F.T., Belleville, R.E., and Wikler, A. Use of differential bar-pressing rate of rats for screening analgesic drugs: I. Techniques and effects of morphine. J. Pharmacol. Exp. Ther., 1957, 120, 388-397.

Kelleher, R.T. and Morse, W.H. Determinants of the specificity of behavioral effects of drugs. Ergeb. Physiol., 1968, 60, 1-56.

Kreuger, H., Eddy, N., and Sumwalt, N. The pharmacology of the opium alkaloids. Pub. Hlth. Reports Suppl. No. 165, Pt. I, Washington, D.C. U.S.G.P.O., 1941.

McMillan, D.E. and Morse, W.H. Some effects of morphine and morphine antagonists on schedule-controlled behavior. J. Pharmacol. Exp. Therap., 1967, 157, 175-184.

Thompson, T. and Schuster, C.R. Behavioral Pharmacology. Englewood Cliffs, N.J.: Prentice Hall, 1968.

Tsou, K. Effects of morphine upon several types of operant conditionings in the rat. Acta. Physiol. Sinica, 1963, 26, 143-150.

Weiss, B. The effects of various morphine-N-allyl-normorphine ratios on behavior. Arch. Int. Pharmacodynam. Therap., 1956, 105, 381-388.

Wikler, A. Sites and mechanisms of action of morphine and related drugs in the central nervous system. Pharmacol. Rev., 1950, 2, 435-506.

Woods, J.H. Effects of morphine, methadone, and codeine in schedule--controlled behavior in the pigeon and rhesus monkey. Fed. Proc., 1969, 28, 511.

FOOTNOTE

[1] This research was supported in part by U.S.P.H.S. Research Grant MH-15349 to the University of Minnesota.

FIGURE LEGENDS

Figure 1. Mean overall response rates on FR 10, FR 20, and FR 40 schedules treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Each mean is based on three values, and ranges are indicated by vertical lines.

Figure 2. Cumulative records of performance on FR 10, FR 20, and FR 40 schedules, treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Five hundred responses were required for each vertical excursion of the recording paper and each session was one hour.

Figure 3. Mean overall response rates on VR 10, VR 20, and VR 40 schedules treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Each mean is based on three values, and ranges are indicated by vertical lines.

Figure 4. Cumulative records of performance on VR 10, VR 20, and VR 40 schedules, treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Five hundred responses were required for each vertical excursion of the recording paper and each session was one hour.

Figure 5. Mean overall response rates on FI 15 sec., FI 30 sec., and FI 120 sec. schedules treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Each mean is based on three values, and ranges are indicated by vertical lines.

Figure 6. Cumulative records of performance on FI 15 sec., FI 30 sec., and FI 120 sec. schedules, treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Five hundred responses were required for each vertical excursion of the recording paper and each session was one hour.

Figure 7. Mean overall response rates on VI 15 sec., VI 30 sec., and VI 120 sec. schedules treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Each mean is based on three values, and ranges are indicated by vertical lines.

Figure 8. Cumulative records of performance on VI 15 sec., VI 30 sec., and VI 120 sec. schedules, treated with saline, 1.0, 3.0, and 6.0 mg/kg of morphine sulfate I.P. Five hundred responses were required for each vertical excursion of the recording paper and each session was one hour.

Figure 9. Scatter diagram of relation between mean baseline response rate under saline and mean rate following administration of 1.0, 3.0, or 6.0 mg/kg of morphine.

Figure 10. The mean percent change from the baseline saline rate for the four simple schedules, in which all values of a given schedule were summed, following administration of 1.0, 3.0, and 6.0 mg/kg of morphine.