

# THE EFFECT OF METHAMPHETAMINE ON OPERANT LEVEL AND AVOIDANCE BEHAVIOR

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Previously, various investigators have reported increases in the rate of avoidance responding (1) due to the administration of amphetamine or methamphetamine (3,5). This paper reports seven experiments concerning various aspects of this effect.

## METHOD

Individual differences in experimental conditions will be described as they occur. The following conditions were common to all of the experiments to be reported.

The subjects were male rats, 6 months to 1 year old, maintained on free food and water in individual living cages.

The apparatus consisted of four experimental cages, 10 inches long, 5 inches wide, and 9 inches high. During an experimental session a No. 313 G.E. light bulb was lit, which was mounted 1/2 inch above the lever behind a 1-inch-diameter transparent window in one end wall of the cage. Each cage was enclosed in a light-proof and sound-resistant box. A sound mask of white noise was continuously fed into the experimental cubicle (75 decibels).

Methamphetamine hydrochloride dissolved in distilled water was injected by subcutaneous route only.

## EXPERIMENT I

The purpose of this experiment was to determine if an increase in the rate of responding, due to the administration of methamphetamine, could be obtained during the first training session on an avoidance procedure before the avoidance response was well-conditioned.

### *Method*

**Subjects:** Six naive albino rats

**Apparatus:** The lever was manufactured commercially<sup>1</sup>. It was center-mounted 2 1/2 inches above the grid floor of the experimental cage. Shocks were of 0.2-second duration at 90 volts A.C. through a 33,000-ohm resistor.

**Procedure:** Avoidance schedule: SS = 5 seconds, RS = 20 seconds (2). Session length: 6 to 8 hours. Drug was administered at various times after the start of the first training session. The animals had no previous experience with the experimental cage.

### *Results and Discussion*

Figure 1 shows the result of methamphetamine administration for one animal, and Table 1 the result for two others.

In all three cases, methamphetamine produced an increase in the rate of responding and, consequently, a decrease in the number of shocks received. The effect of

<sup>1</sup> R. Gerbrands, 96 Ronald Road, Arlington, Massachusetts

the drug was reversible. After a few hours of an increased rate of responding, the animals returned to their previous "poor" performance.

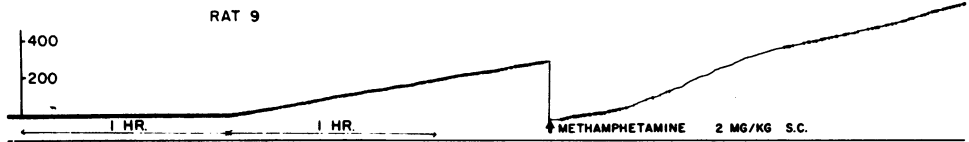


Figure 1. Effect of methamphetamine on rate of responding during the first training session on an avoidance procedure. The vertical marks indicate the occurrence of shocks. The drug was administered at the arrow.

The other three animals used in this experiment showed no increase in rate. Methamphetamine was administered before these animals consistently made one or two lever presses immediately after each shock, a phenomenon that occurs frequently during the initial training session on the avoidance procedure used in this experiment. A dose of 1 milligram per kilogram was administered to two of these rats 20 minutes after the start of the experiment. A dose of 2 milligrams per kilogram was given to the third rat 30 minutes after the start of the experiment. None of

Table 1  
The Effect of Methamphetamine During the  
Course of an Experimental Session

Rat 31		
Successive Time Periods in Minutes	Responses per Minute	Shocks per Minute
0 - 40*	3.7	2.7
40 - 110	4.3	1.4
110 - 180	5.4	1.3
180 - 240	4.3	2.2
240 - 300	4.8	2.2
300 - 360	3.2	2.3
360 - 420	3.3	2.4
*MPT, 1 mgm. /kgm. , injected 40 minutes after start of experiment.		
Rat 34		
0 - 75*	3.5	4.5
75 - 145	4.3	1.5
145 - 215	5.4	0.9
215 - 280	6.1	1.5
280 - 340	5.0	2.0
340 - 400	3.8	2.3
*MPT, 1 mgm. /kgm. , injected 75 minutes after start of experiment.		

these three animals made a single response during 8 hours after drug administration.

#### EXPERIMENT II

Experiment I demonstrated that increases in the rate of responding could be obtained even during the first session of training. The purpose of the following experiments was to determine whether comparable rate increases could be obtained with methamphetamine during unconditioned responding.

#### Method

Subjects: Twelve naive albino rats

Apparatus: Identical to Experiment I.

Procedure: In Experiment IIA, six rats were subjected to a 1-hour session on two successive days. A dose of 1.5 milligrams per kilogram of methamphetamine was administered on the first day only, 15 minutes before the start of the session. In Experiment IIB, six rats were given 1-hour operant-level sessions on five consecutive days. A dose of 2.5 milligrams per kilogram of methamphetamine was administered on the fourth day only, 15 minutes before the start of the session.

#### Results and Discussion

The total number of responses made by each animal during the operant-level sessions of Experiment IIA and B are shown in Table 2. At 1 milligram per kilogram, methamphetamine had no noticeable effect on operant-level responding. This same dose increased the rate of lever pressing in Experiment I for those animals

Table 2

The Effect of Methamphetamine on the Number of Responses  
Emitted During 1-hour Operant-level Sessions

		<u>Experiment A</u>					
		Rat : <u>1</u> <u>2</u> <u>3</u> <u>4</u> <u>5</u> <u>6</u>					
Session 1	1.5 mgm. /kgm.	2	0	0	1	0	3
Session 2	no drug	0	0	1	0	0	1
		<u>Experiment B</u>					
		Rat : <u>7</u> <u>8</u> <u>9</u> <u>10</u> <u>11</u> <u>12</u>					
Session 1	no drug	2	0	2	6	2	1
Session 2	no drug	0	0	0	2	2	2
Session 3	no drug	0	0	0	4	0	1
Session 4	2.5 mgm. /kgm.	5	26	9	41	2	0
Session 5	no drug	10	0	5	1	1	1

in which the avoidance contingency had taken effect. At a dose of 2 1/2 milligrams per kilogram the rate of unconditioned responding increased but the order of magnitude of the increased level of responding was still only 10 to 50% of the increase observed in the avoidance procedure.

#### EXPERIMENT III

This experiment is a replication of Experiments I and II and was intended to determine the effect of methamphetamine on operant-level responding and, subsequently, on the rate of responding in an avoidance procedure on the same animals.

Subjects: Six naive hooded rats (Long-Evans strain) (No. 01 through 06)

Apparatus: Identical to Experiments I and II, except that the lever was made from a Switchcraft No. 3002 Lev-R type switch and that shocks were of 0.2-second duration at 1 milliamperes as provided by a constant-current stimulator.

Procedure: The general procedures during the operant-level phase and the avoidance-conditioning phase were similar to those described for Experiments I and II. Details concerning the experimental schedule and the number of operant-level sessions can be determined from Table 3. An avoidance training session was given 3 days after the last operant-level session.

#### Results and Discussion

The total number of responses made by each animal during the operant-level sessions is shown in Table 3. In this experiment neither a dose of 2 milligrams per kilogram or 4 milligrams per kilogram had a noticeable effect on the operant-level responding.

Table 3

The Effect of Methamphetamine on the Number of Responses Emitted During 1-hour Operant-level Sessions

Dose mgm. /kgm.	Session	Rat Number					
		01	02	03	04	05	06
--	1	49	21	1	8	12	3
--	2	7	38	2	0	0	0
--	3	0	4	0	0	2	0
--	4	0	2	1	0	1	0
--	5	0	6	1	0	1	0
--	6	3	7	0	1	0	0
--	7	2	2	1	0	0	0
2	8	4	0	1	0	0	0
--	9	0	5	1	0	0	0
--	10	0	0	2	0	0	0
--	11	0	5	0	0	0	0
4	12	0	0	0	0	0	0

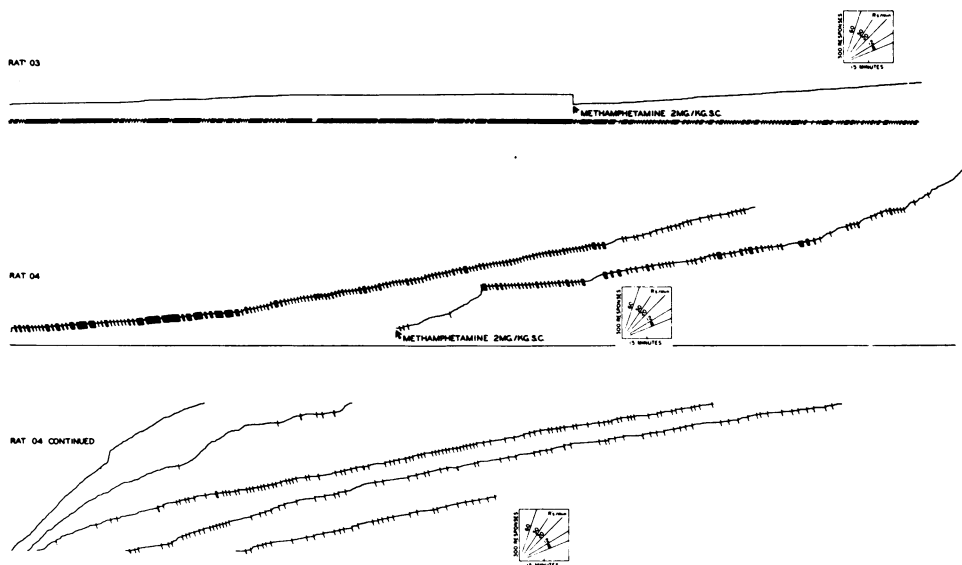


Figure 2. Effect of methamphetamine on rate of responding during the first session on an avoidance procedure. The vertical marks on the base line of the record of Rat 03 and on the cumulative record of Rat 04 indicate the occurrence of shocks. The drug was administered at the arrows.

Figure 2 shows the effect of 2 milligrams per kilogram of methamphetamine on the rate of responding of Rats 03 and 04 in the avoidance situation. These were the only animals to show an increase in rate. With the other four animals the drug was deliberately administered at a time that was judged too early as determined by inspection of the cumulative records. The present data, and those of Experiments I and II, clearly show that the large increases in rate observed after methamphetamine administration cannot simply be due to an increase in "general activity" or unconditioned responding. It is concluded that substantial rates of responding can only be induced by the drug after the avoidance contingency has started to take effect.

#### EXPERIMENT IV

The purpose of this experiment was to investigate the effects of various doses of methamphetamine on the rate of responding.

Subjects: 1 albino rat (No. 11). Experimental history: avoidance training for approximately 60 hours.

1 albino rat (No. 15). Experimental history: avoidance training for approximately 150 hours.

Apparatus: Identical to that used in Experiment I.

Procedure: Avoidance procedure: SS = 5 seconds, RS = 20 seconds (2). Experimental sessions carried out on alternate days or nights. Drug was administered 2 hours after the beginning of a session. Four to five days intervened between successive drug sessions. Day sessions were 7 hours long; night sessions, 9 hours.

### Results and Discussion

The effect of 2 milligrams per kilogram of methamphetamine on the performance of Rat 11 is shown in Fig. 3. The numbers of responses emitted, as well as the numbers of shocks received during successive half-hour periods, are indicated respectively below and on top of the cumulative-response curve. The record shows that Rat 11 was a relatively poor performer under the conditions of the experiment.

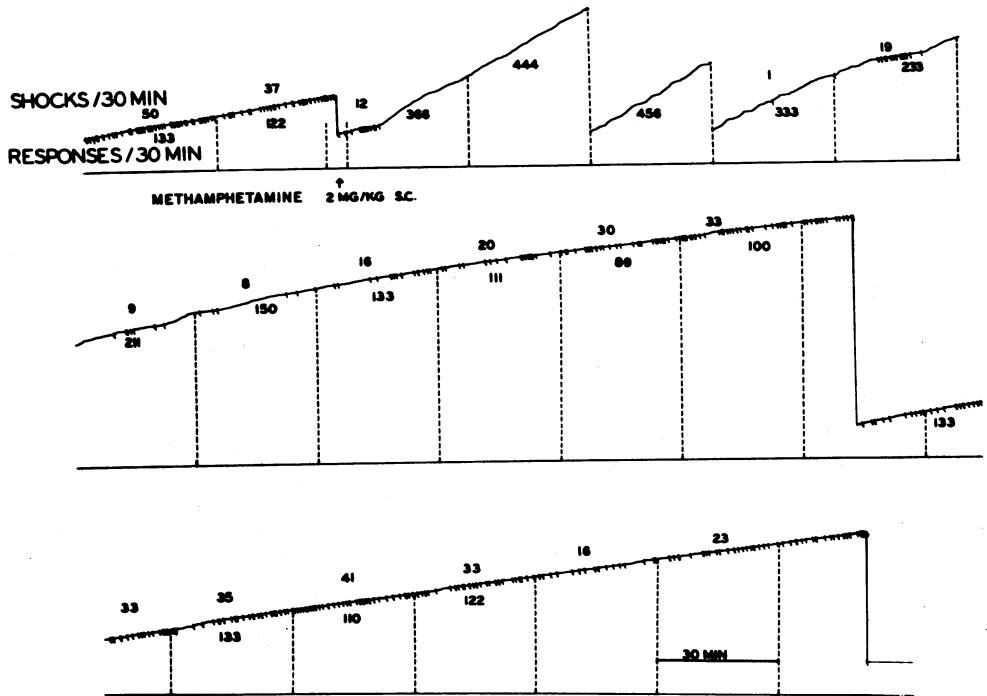


Figure 3. Effect of methamphetamine on rate of responding after approximately 60 hours of training on an avoidance procedure. The vertical marks indicate the occurrence of shocks. The drug was administered at the arrow.

(Compare with Reference 4, Fig. 7.) The injection itself had little effect. Approximately 10 minutes after injection, however, the rate increased, and it more than tripled during the following 2 hours. The effect was temporary, and after approximately 4 1/2 hours the animal had returned to its pre-drug performance.

The data of Rat 15 are presented in Table 4. At 1 milligram per kilogram, methamphetamine produced a complete suppression of the avoidance behavior. During the first half-hour after injection of 1 milligram per kilogram or 2 milligrams per kilogram, there was an increase in rate with few shocks followed by a great decrease in rate with many shocks. When the experiment was temporarily stopped, and the animal left in the cage for a period of time, the rate again increased considerably compared with the pre-injection control level. The period of time out presumably permitted the effects of the overdose to dissipate.

Table 4

Effect of Three Doses of Methamphetamine During  
Successive Hours on Performance of Rat 15

	0.65 mgm. /kgm.		1 mgm. /kgm.		2 mgm. /kgm.	
	Resp. /hr.	Sh. /hr.	Resp. /hr.	Sh. /hr.	Resp. /hr.	Sh. /hr.
Control	398	92	394	45	597	84
	218	87	355	48	457	66
Post- Injection	727	9	277	228	358	350**
	553	32	0	720	T.O.	T.O.
	349	78	0	360*	T.O.	T.O.
	302	127	488	37	T.O.	T.O.
	---	---	---	---	757	18
	---	---	---	---	585	13

\* Experiment turned off 30 minutes after start of third hour following injection .  
Animal kept in time out for remaining 30 minutes of third hour after injection.

\*\* Experiment turned off 30 minutes after start of first hour following injection.  
Animal kept in time out for next 3 1/2 hours.

The critical dose level above which methamphetamine produces a decrease in the rate of responding differs from animal to animal. It varies also for the same animal during different sessions. When a dose of 1 milligram per kilogram was administered again to Rat 15, for example, the rate of responding almost doubled during the two hours following drug administration. (See Fig. 4.) There is no evidence of a

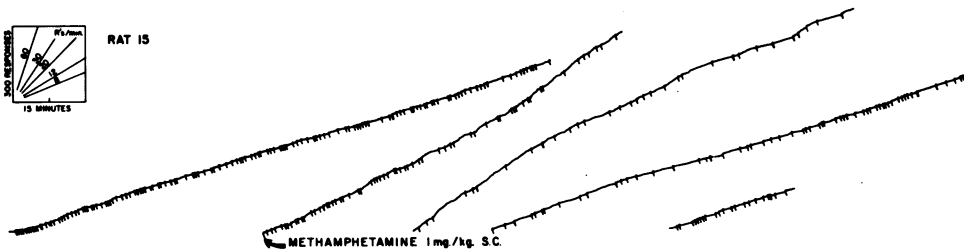


Figure 4. Effect of methamphetamine on rate of responding on an avoidance procedure (after approximately 90 hours of training). The vertical marks indicate the occurrence of shocks. The drug was administered at the arrow.

depression of the rate of responding at any time after injection. (The numbers of responses emitted were 333, 345, 648, 622, 430, 319, and 342; and the numbers of shocks received during successive hours were 87, 67, 57, 26, 27, 27, and 55. The drug was administered at the end of the second hour of the session.)

#### EXPERIMENT V

The data of this experiment were obtained after the previously described experiments. The experimental conditions were identical to those of Experiment IV, ex-

cept that a modified Switchcraft switch was used as a lever. The purpose of the experiment was to investigate the effects of various doses of methamphetamine using this type of lever.

### Results and Discussion

The effects of various doses of methamphetamine are shown in Fig. 5 and 6. Saline was administered during the fourth session, but without a noticeable effect. The performance of the animal at this stage was still "poor." During Sessions 7, 11, and 12, no drug was administered. The effect of 3 milligrams per kilogram ad-

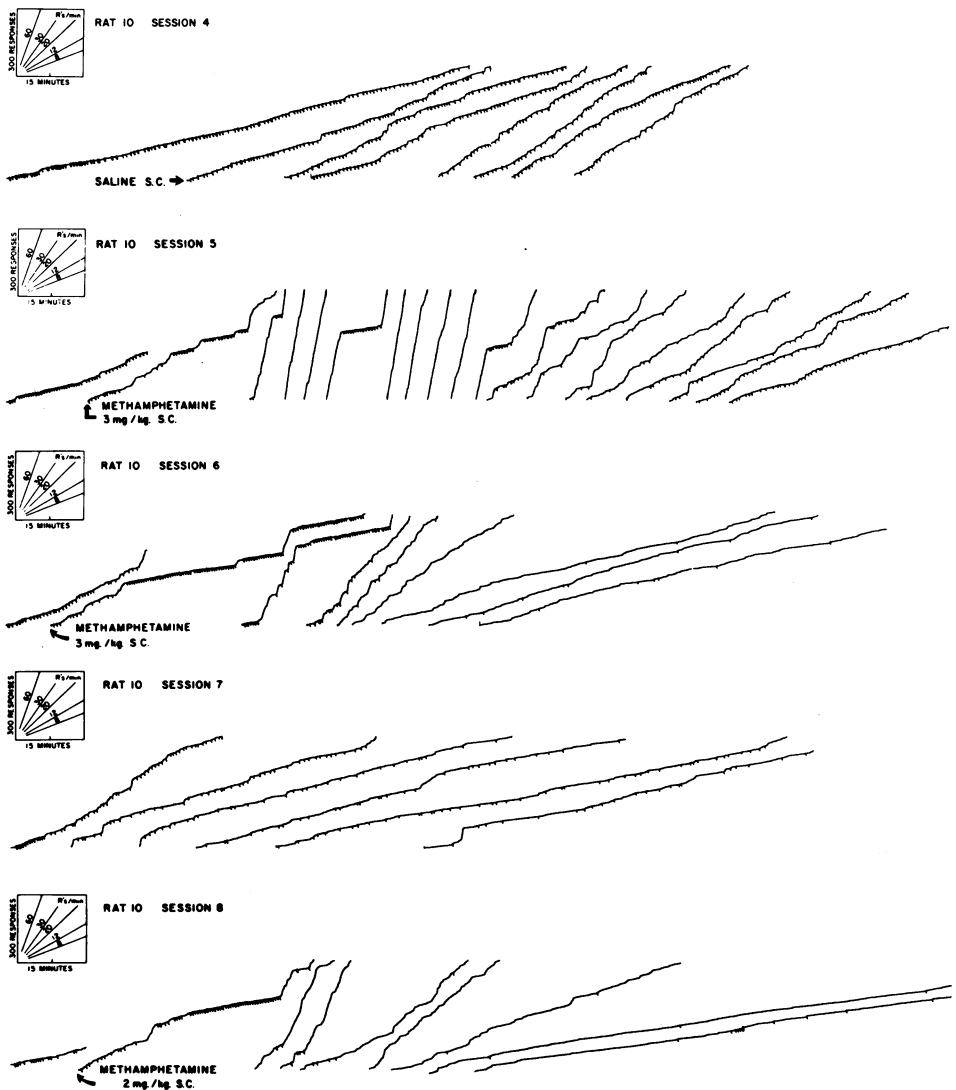


Figure 5. Effect of various doses of methamphetamine on avoidance responding. The vertical marks indicate the occurrence of shocks. The drug was administered at the arrows.



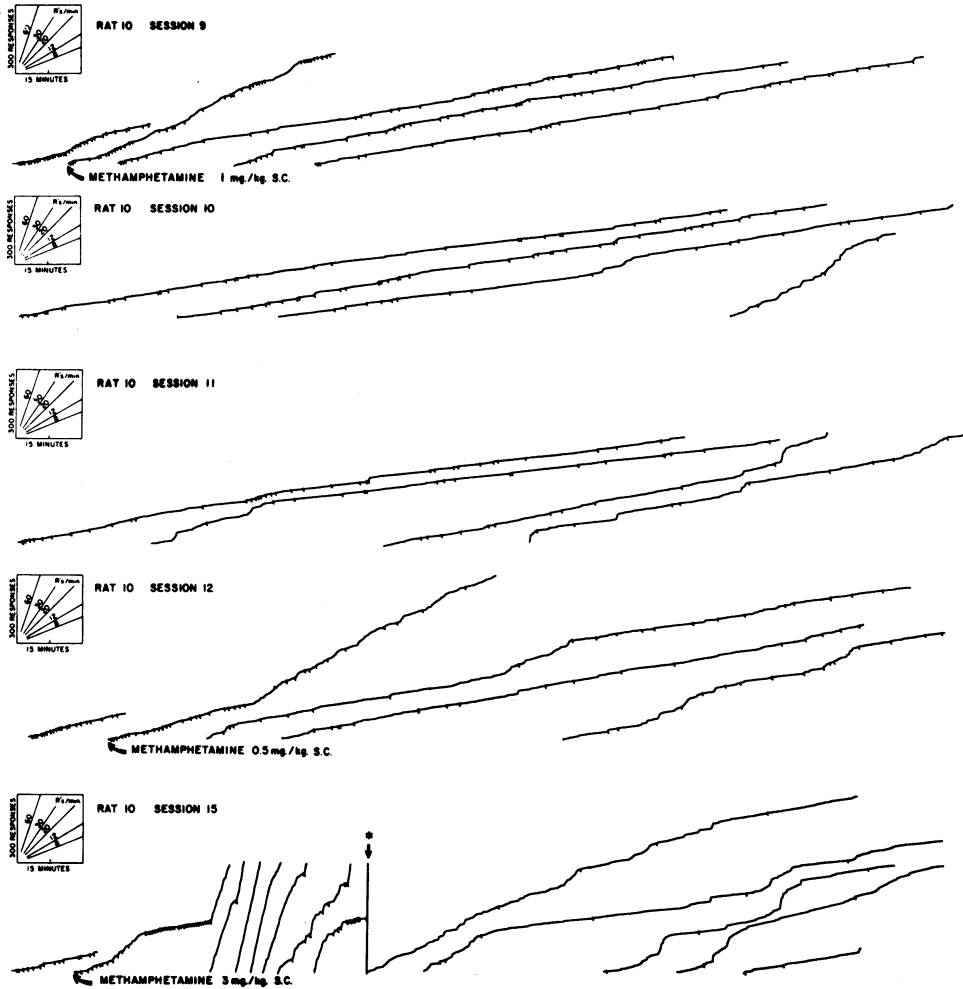


Figure 6. Effect of various doses of methamphetamine on avoidance responding. The vertical marks indicate the occurrence of shocks. The drug was administered at the arrows.

ministered during Session 5 was to increase the rate of responding approximately tenfold. No increase of a comparable magnitude had ever been observed with methamphetamine with the type lever used in Experiment I. A dose of 3 milligrams per kilogram had previously invariably produced an extended breakdown of responding.

Administration of another 3-milligrams-per-kilogram dose of methamphetamine during the next session 3 days later again produced a large increase in the rate of responding. The magnitude of the effect, however, was approximately half of that obtained during Session 5. This is due to a tolerance effect. When a dose of 3 milligrams per kilogram was administered during Session 15, 7 days after administration of a dose of 0.5 milligram per kilogram, the effect was of comparable magnitude to that observed during Session 5. During Session 15 a temporary apparatus

failure of approximately 60 minutes occurred at the arrow with the asterisk. During this period the animal was in the pre- and post-session time-out condition (cage dark). The rate increase observed after 1 milligram per kilogram during Session 9 is also considerably less than that observed after 0.5 milligram per kilogram during Session 12. Session 9 was given 2 days after Session 8, during which 2 milligrams per kilogram was administered. The occurrence of a tolerance effect has been observed repeatedly. A separate publication will deal extensively with the problem.

The present data still show temporary depressions of responding at doses of 3 milligrams per kilogram (Sessions 5, 6, and 15). After a dose of 4 milligrams per kilogram the animal completely stopped responding. This is a considerably larger dose than the one which produced complete cessation of responding in Experiment IV. It is conceivable that the use of an operant with a different topography could have increased the magnitude of the effect of methamphetamine observed here. The partial or complete depressions of the rate observed in these experiments seem to be produced by the physical limitations of the conditions under which an animal is responding.

#### EXPERIMENT VI<sup>2</sup>

The late effect of an overdose after a time out, as observed in Experiments IV and V at doses of 4 milligrams per kilogram, necessitated a control experiment. What is the effect on the rate of responding of giving an animal 350 shocks, putting him in a time out for 3 1/2 hours, and then restarting the avoidance procedure *in the absence of the drug*?

The subjects were three rats with an experimental history of avoidance training for approximately 120 hours.

The apparatus and the procedure were identical to that of Experiment V, except that the RS interval was 30 seconds. During the unavoidable shock periods, shocks were given every 5 seconds.

#### *Results and Discussion*

Figure 7 shows the data of Rat K9 during 5 sessions. At the arrows, 150 shocks and a subsequent time out of 3 hours, 100 shocks and a time out of 2 hours, and 450 shocks and a time out of 5 minutes were given during Sessions 5, 6, and 11, respectively. At no time was a post time-out increase in *rate* observable. The data on the other two animals, which also received between 50 and 500 shocks and time outs of 5 minutes to 4 hours, were similar in this respect and will not be presented here. The effects of an overdose of methamphetamine following a time out were apparently due to the drug itself.

One effect of the administration of unavoidable shocks proved to be extremely long-lasting. It occurred in all three animals and is illustrated by comparing the performances of Rat K9 during Sessions 3 and 4 and Session 7. The performance during Session 7 is characterized by bursts of extremely rapid responding which tend to occur after a period of "successfully timed" responding. This behavior, which appeared during Session 6, still characterized Rat K9 after 29 undisturbed 7-hour sessions on the same schedule. It seems plausible that it represents another

<sup>2</sup>This experiment was suggested to the author by Dr. P. B. Dews.

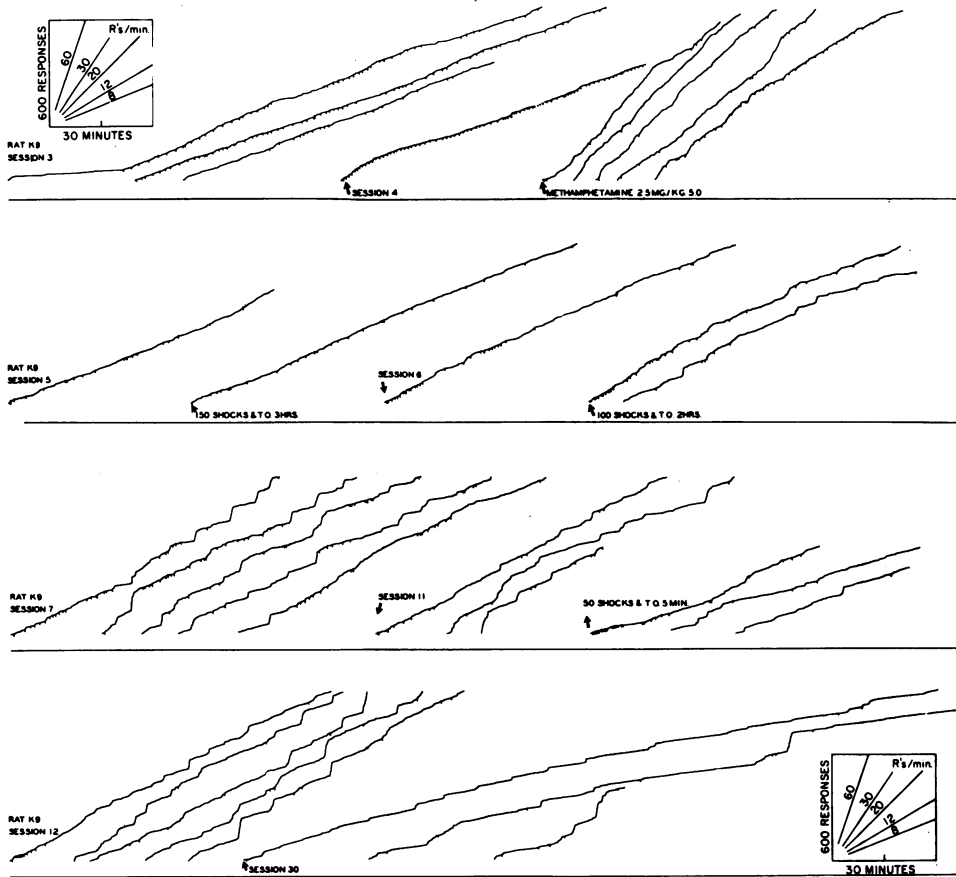


Figure 7. The effect of the administration of unavoidable shocks followed by time out on the avoidance responding of a rat. The vertical marks indicate the occurrence of shocks. Unavoidable shocks followed by a time out occurred at the arrows.

example of superstitious responding (4). The unavoidable shocks were given by disconnecting the keyer from the circuit that started and reset the RS timer. During the unavoidable shock period, with shocks given at a rate of 1 every 5 seconds, *the animal responded at a considerably higher rate than that emitted during the regular avoidance procedure*. The shock period, which at the longest lasted approximately 30 minutes, was invariably followed by a time out *up to 4 hours*. The time out from the type of avoidance schedules used here is presumably reinforcing. In the present case the time out presumably selectively reinforced a high rate of responding.

#### EXPERIMENT VII

The purpose of this experiment was to assess the variability of the effects of methamphetamine administration in the individual animal from session to session when a sufficient length of time intervenes between sessions to eliminate the temporary tolerance observed during Experiment V.

### Method

Subjects: 4 rats. Experimental history: Avoidance training for approximately 180 hours.

Apparatus: Identical to Experiment I.

Procedure: 1 milligram per kilogram of methamphetamine was administered four times after a 2-hour control period to each of the four rats. One night session, during which no drug was administered, and 4 to 5 days intervened between each drug session. The session length was 7 hours.

### Results and Discussion

The numbers of responses per hour during successive hours for the drug runs of each rat are presented in Fig. 8. For each rat, 1 milligram per kilogram of methamphetamine produced a large increase in rate. In Rats 16 and 20 the initial

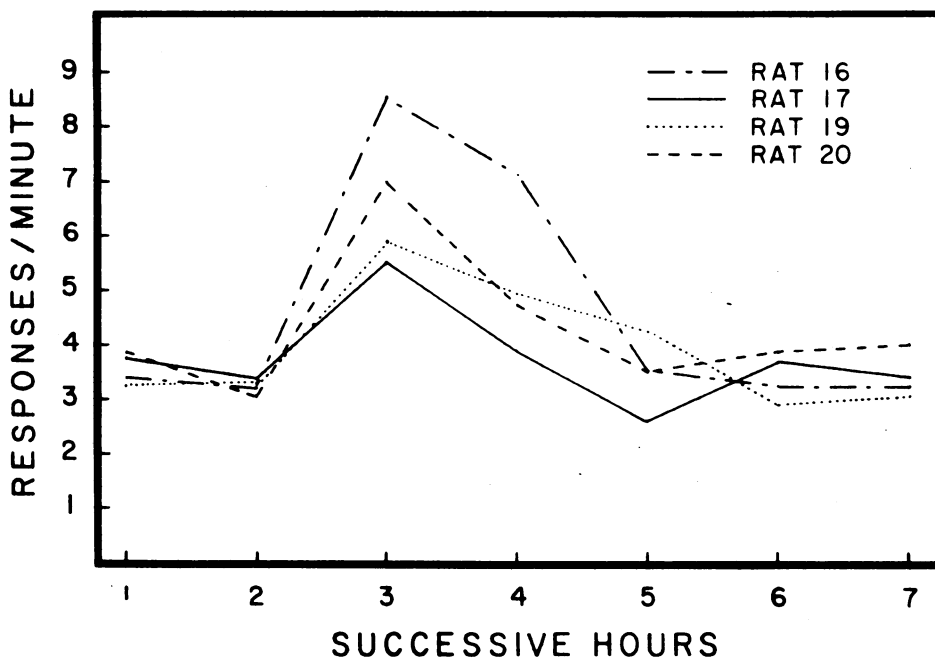


Figure 8. Mean number of responses per minute for each of four rats during 7 successive hours. One milligram per kilogram of methamphetamine was administered at the end of the second hour. Each point is based on four observations.

control rate was more than doubled. In all cases, the rate has returned to the base line 3 hours after drug administration. A decrease in rate after the initial increase occurred frequently. This may be similar to the post-stimulation depression period commonly observed in other situations after methamphetamine administration.

The data show that the effects of methamphetamine can be consistent from animal to animal and from session to session in the same animal.

Table 5, which presents the average data for the animals, shows that the variability is relatively minor. The present procedure could be used as a simple assay for

Table 5

Number of Responses per Hour During Successive Hours Before and After Administration of 1 mgm. /kgm. of Methamphetamine.

Averaged data of Rats 16, 17, 19, and 20.

	Mean	S. E.
Pre-drug	336.8	8.5
Control	310.6	7.4
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Post-drug	730.3	39.4
	572.9	42.2
	376.3	26.8
	332.9	20.8
	333.6	21.9

estimating potency and duration of methamphetamine and analogues in individual animals.

#### SUMMARY AND CONCLUSIONS

A series of experiments has been reported concerning the effect of methamphetamine on avoidance behavior. It has been demonstrated that:

1. Methamphetamine can produce large increases in the rate of responding even early in training.

2. This effect is not due to an increase in "general activity" or unconditioned responding.

3. Temporary periods of depression of responding occur at higher doses, and still larger doses will completely eliminate responding temporarily.

4. The specific dose at which this depression effect occurs depends on the type of lever used.

5. The effect of an intermediate dose, if appropriately spaced to eliminate the occurrence of a temporary tolerance effect, is reproducible for an individual animal.

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