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Self-Administration of Amphetamine and Cocaine by Rats

by

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Abstract

Rats were conditioned to intravenously self-administer d-amphetamine or cocaine or fixed ratio reinforcement schedules. Response frequency was studied as a function of dosage per infusion (reinforcement magnitude) and the number of responses required per infusion (fixed ratio size). Frequency of self-administration was found to vary inversely as a function of drug dosage. The frequency of responding varied directly as a function of the value of the fixed-ratio schedule of amphetamine reinforcement, while the number of infusions per hour remained essentially unchanged.

The prolonged self-administration of drugs by animals has been regarded as an instance of operant conditioning, in which the drug serves as a reinforcer for the behavior that leads to drug injection. Thus, while such drugs as morphine, codeine, cocaine, amphetamine, pentobarbital, and ethanol are known to be self-administered by animals (Deneau, Yanagita, and Seevers, 1964), only morphine has been used in attempts to systematically determine the factors which influence drug reinforcement (Davis and Nichols, 1962; Thompson and Schuster, 1964; Weeks, 1962). The present experiment investigates certain reinforcement factors which may influence the self-administration of amphetamine and cocaine. The effects of magnitude of reinforcement (drug dosage per infusion) on the self-administration of amphetamine and cocaine, and the effects of the contingencies for drug reinforcement on the self-administration of amphetamine were determined. These factors were selected for study because they have been shown to affect the self-administration of morphine (Weeks, 1962), and are known to affect the maintenance of other operantly conditioned responses.

Method

Subjects

The subjects were six male albino rats of the Holtzman strain. They were 120-180 days old and weighed 300-500 gm. at the start of the experiment. Five of the subjects were used for amphetamine self-administration and one subject was used for cocaine self-administration.

Apparatus

The apparatus was similar to several that have been developed to permit the intravenous self-administration of drugs by unrestrained animals (Davis, 1966; Weeks, 1962). Briefly, it consisted of equipping each subject with a chronic jugular catheter which connected at a shoulder harness to a length of needle tubing that passed out the top of the animal's cage (see Figure 1). The needle tubing was joined to an infusion pump by a swivel and tube arrangement that allowed the animal to move and turn about in the cage. By pressing a lever located on the cage wall, the animal activated the infusion pump and received a 50-sec. intravenous injection of .5 cc of drug solution.

The animal cage was a standard operant conditioning chamber that had been modified to incorporate the infusion apparatus.

The cage contained a continuous supply of food and water, and was located in a ventilated, sound-shielding box. The programming and recording of all experimental events were controlled automatically by electromechanical equipment located in an adjacent room.

Procedure

Following catheterization the subjects were placed in the self-administration cages where they lived for the duratic of the experiment, and allowed to develop a stabilized patterr of responding reinforced by drug infusion. During this time, each lever press delivered a .5 mg/kg infusion of dextro-amphetamine sulfate or cocaine hydrochloride in isotonic saline solution. After drug self-administrations had stabilized, the magnitude of reinforcement (infusion dosage of drug) or the number of responses required to receive reinforcement was varied for each animal. The value of drug dosage ranged from .25 to 1.0 mg/kg/infusion for d-amphetamine, and from .25 to 1.5 mg/kg/infusion for cocaine. The schedule of drug reinforcement, which was varied for d-amphetamine only,

ranged from a fixed-ratio one to a fixed-ratio 30 schedule of reinforcement. That is from one response per infusion, to 30 responses per infusion.

Results and Discussion

A stable pattern of drug self-administration developed for both amphetamine and cocaine within 1-3 days after the subjects were placed in the infusion cages. Throughout the experiment, periods of responding for drug infusion alternated with periods of no responding. The length of the responding and no-responding periods was 24-72 hrs. and 10-24 hrs. for amphetamine, and 12-48 hrs. and 10-18 hrs. for cocaine, respectively. The length of a given period did not seem to be related to the length of the preceding period or to the drug dosage. It was noted that during a no-responding period a period of responding could be initiated by "priming" the animals with a single drug injection.

The effects of magnitude of reinforcement (drug dosage per infusion) on the frequency and patterning of drug self-administrations are shown for amphetamine in Figures 2-7,

and for cocaine in Figures 8 and 9. These data are summarized in Table 1. As can be seen, decreases in drug dosage are associated with increases in self-administrations and increases in dosage are associated with decreases in self-administrations. Thus, for each subject about the same total amount of drug was taken at all dosages. The mean drug intake was .54 mg/kg/hour for the amphetamine animals and 4.8 mg/kg/hour for the cocaine animals.

The effects of varying the value of the schedule of amphetamine reinforcement on response frequency and number of reinforcements are shown in Figures 10-15 and summarized in Table 2. When the value of a fixed-ratio schedule of drug reinforcement was increased, response frequency increased accordingly and the number of drug reinforcements per hour remained about the same. The mean amphetamine intake over all fixed-ratio values was .52 mg/kg/hour.

The finding of an inverse relationship between frequency of drug self-administration and drug dosage, and a direct relationship between the frequency of responding for self-administration and value of fixed-ratio schedule of reinforcement, is in accord other work involving morphine self-administration (Weeks, 1962).

References

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Davis, W. M., and Nichols, J. R. Physical dependence and sustained opiate-directed behavior in the rat. A preliminary report. Psychopharmacologia, 1962, 3, 139-145.

Deneau, G. A., Yanagita, T., and Seevers, M. H. Psychogenic dependence to a variety of drugs in the monkey. Pharmacologist, 1964, 6, 182.

Thompson, T. I., and Schuster, C. R. Morphine self-administration, food-reinforced and avoidance behaviors in Rhesus monkeys. Psychopharmacologia, 1964, 5, 87-94.

Weeks, J. R. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. Science, 1962, 138, 143-144.

TABLE 1

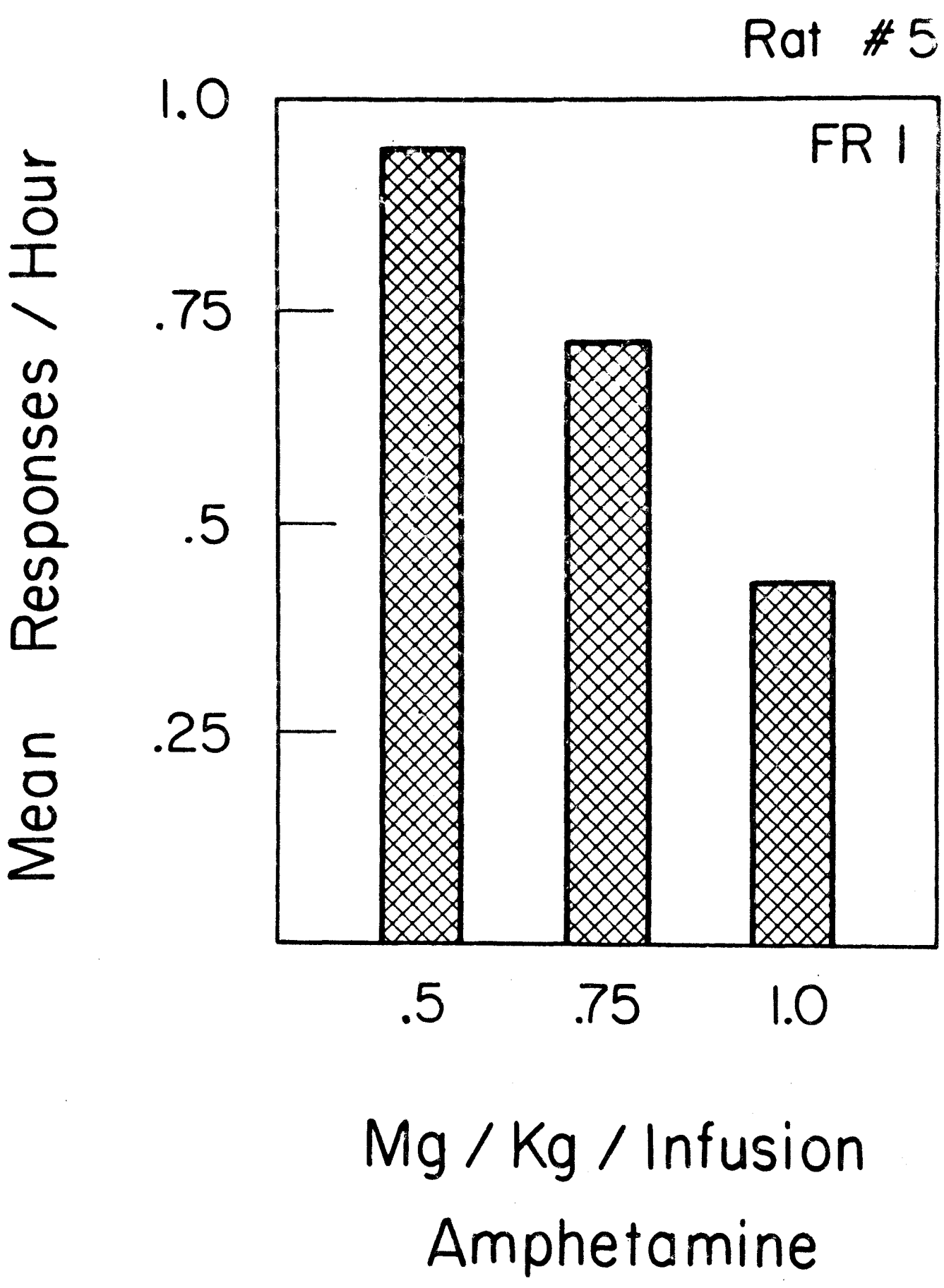
Effects of Magnitude of Reinforcement (Drug Dosage per Infusion) on Amphetamine and Cocaine Self-Administration.

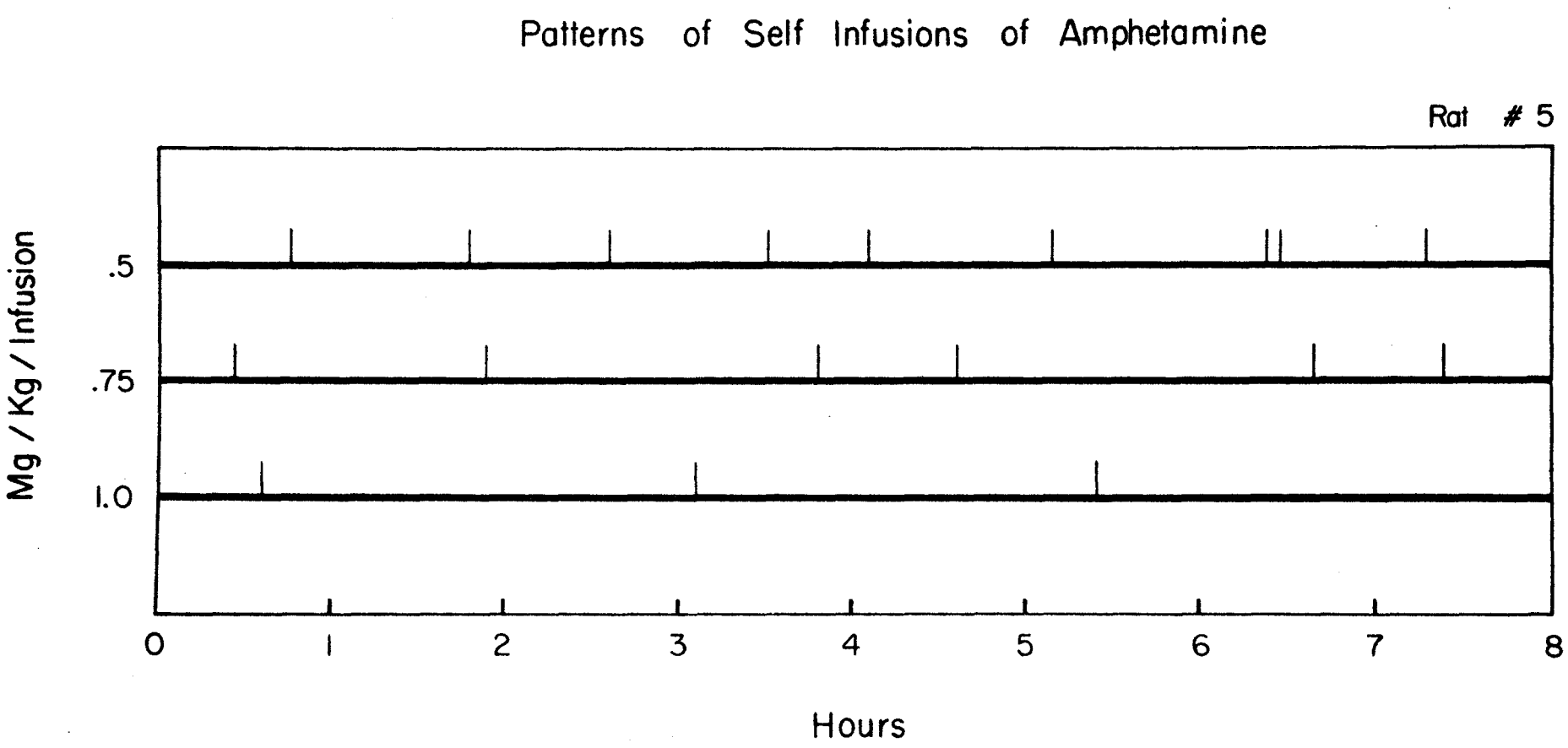
AMPHETAMINE						COCAINE	
Rat #5		Rat #7		Rat #12		Rat #20	
mg/kg Drug	Responses Per Hour	mg/kg Drug	Responses Per Hour	mg/kg Drug	Responses Per Hour	mg/kg Drug	Responses Per Hour
.5	.89	.5	1.2	.5	1.1	.25	11.0
.75	.71	.375	1.8	.375	1.5	.5	8.5
1.0	.42	.25	2.2	.25	2.8	1.0	5.7
				.5	1.1	1.5	4.4

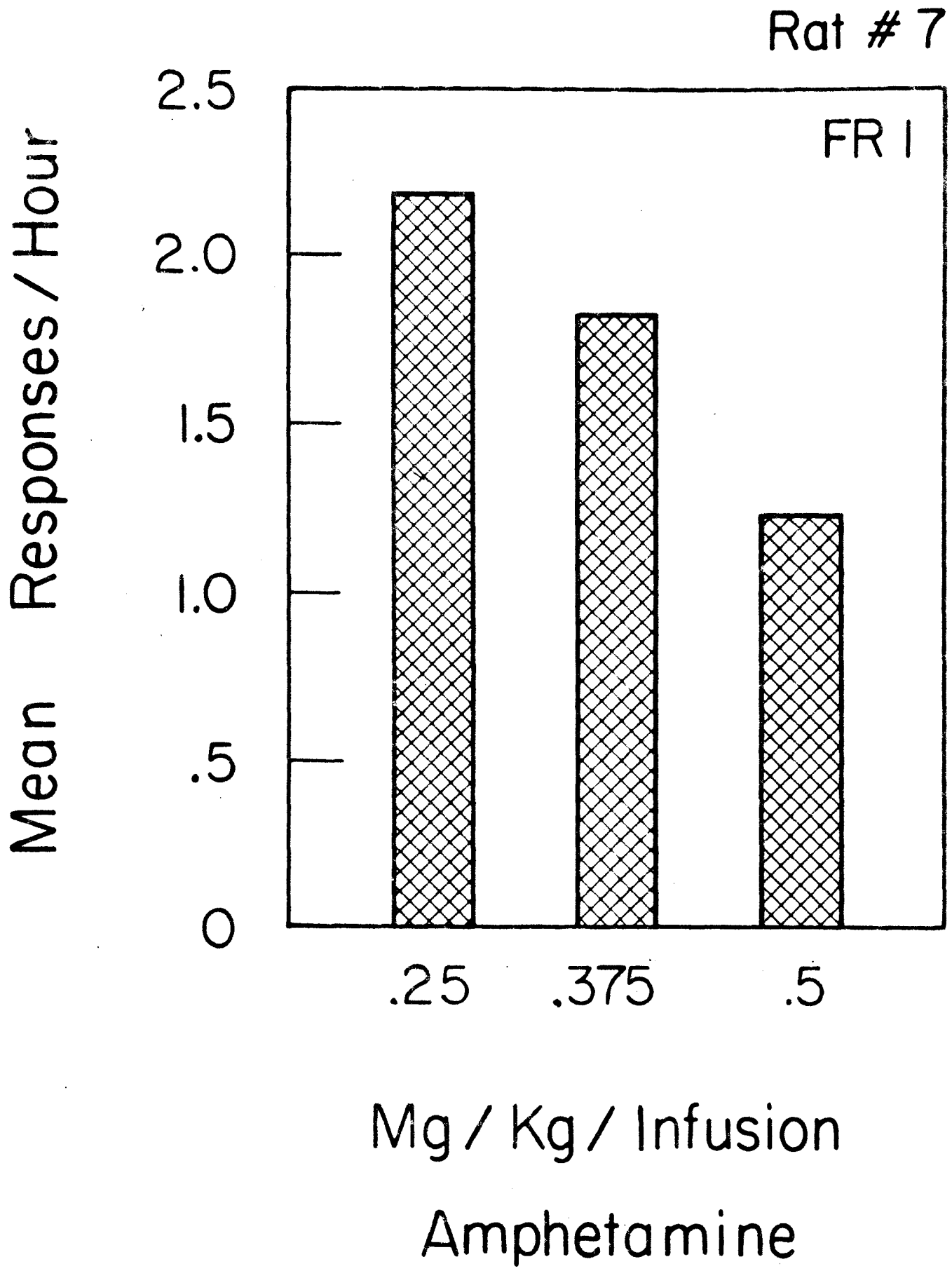
TABLE 2

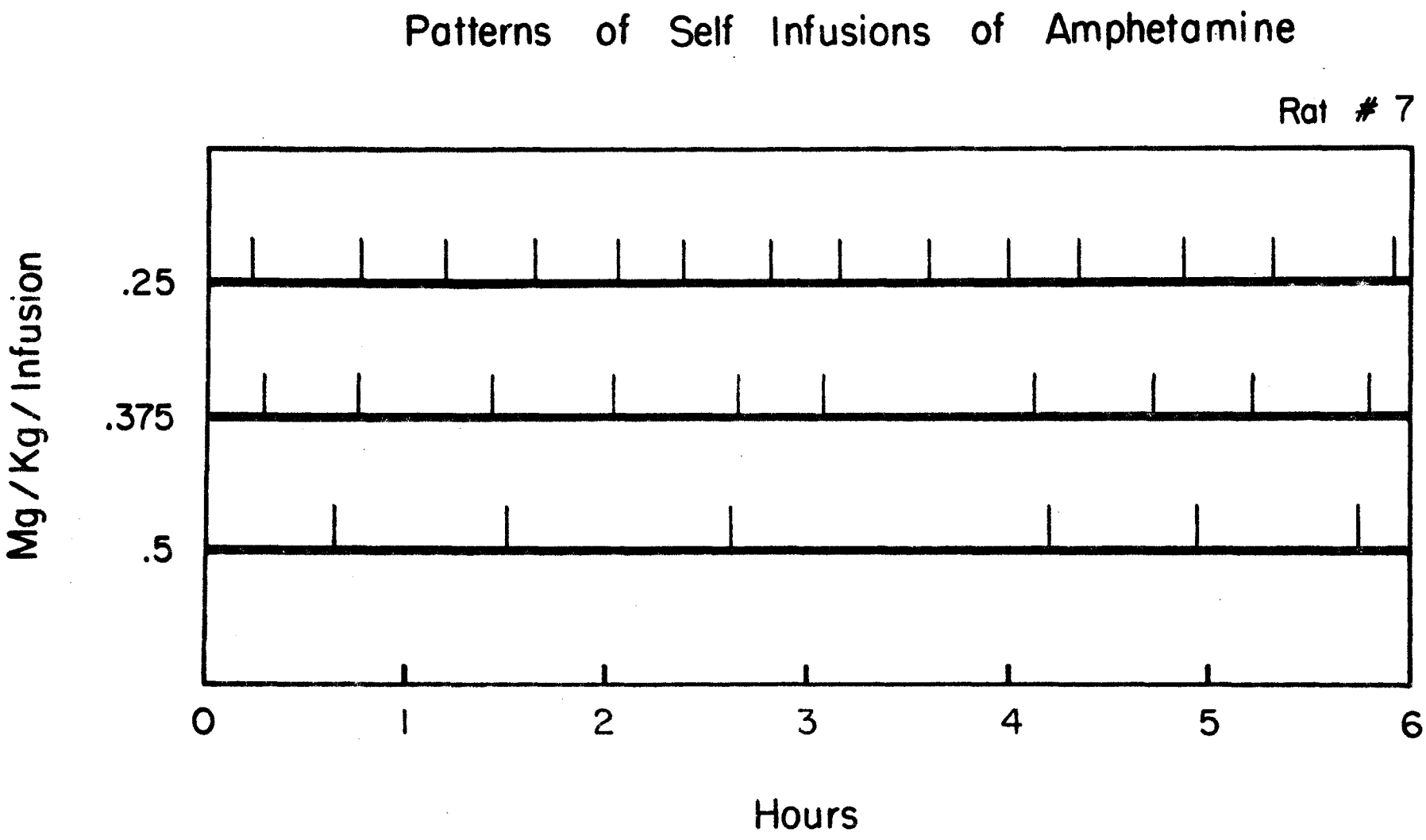
Effects of Intermittency of Reinforcement on Response Rate and Infusion Rate of Amphetamine Self-Administration

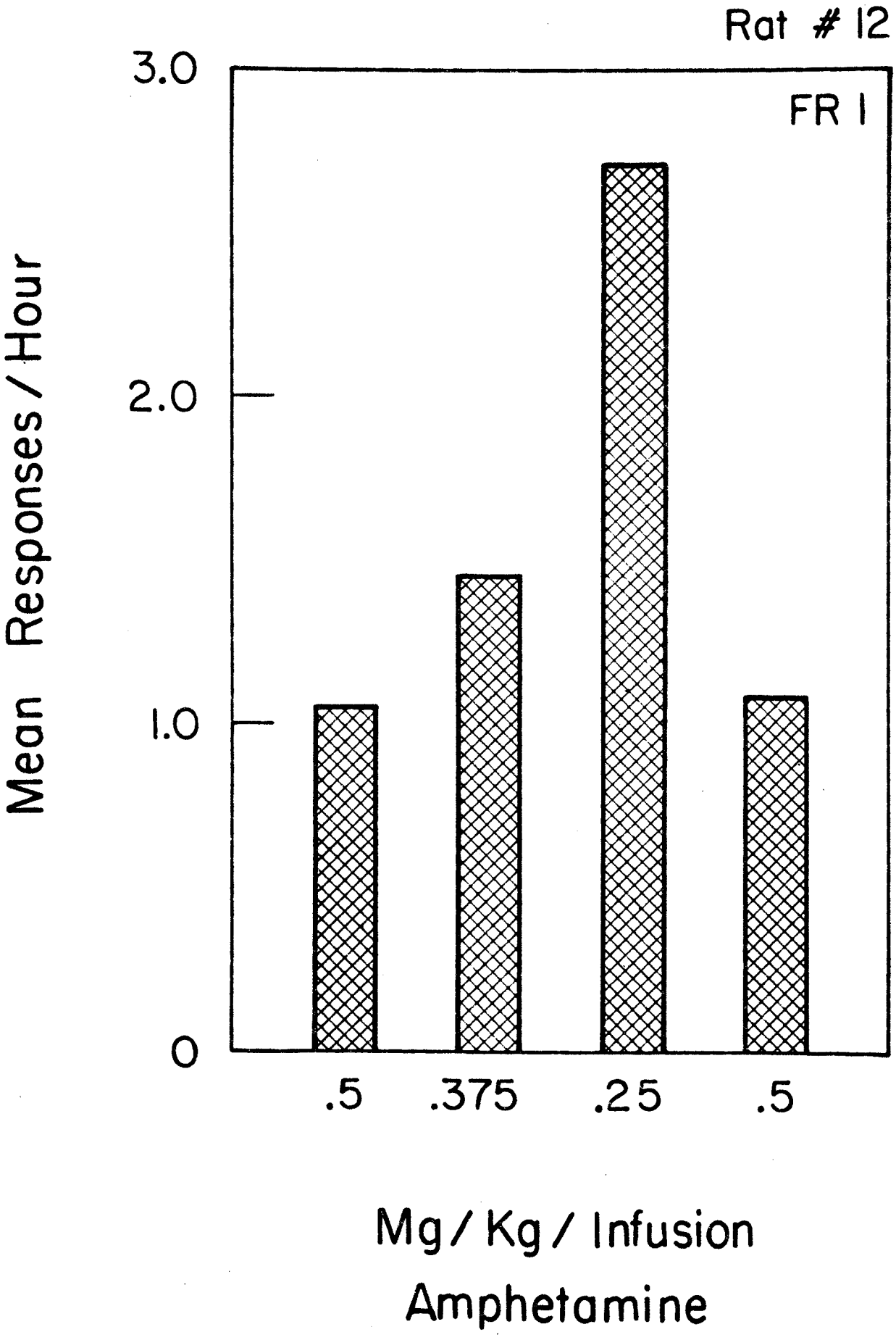
Rat #4			Rat #7			Rat #8		
Fixed-Ratio Schedule	Responses Per Hour	.5 mg/kg Infusions Per Hour	Fixed-Ratio Schedule	Responses Per Hour	.5 mg/kg Infusions Per Hour	Fixed-Ratio Schedule	Responses Per Hour	.25 mg/kg Infusions Per Hour
1	.9	.9	1	1.2	1.2	1	1.7	1.7
5	4.2	.8	2	2.6	1.3	2	2.9	1.4
10	12.6	1.2	3	3.9	1.3	3	4.5	1.5
20	28.1	1.4	5	5.1	1.0	5	7.5	1.5
30	47.1	1.5						

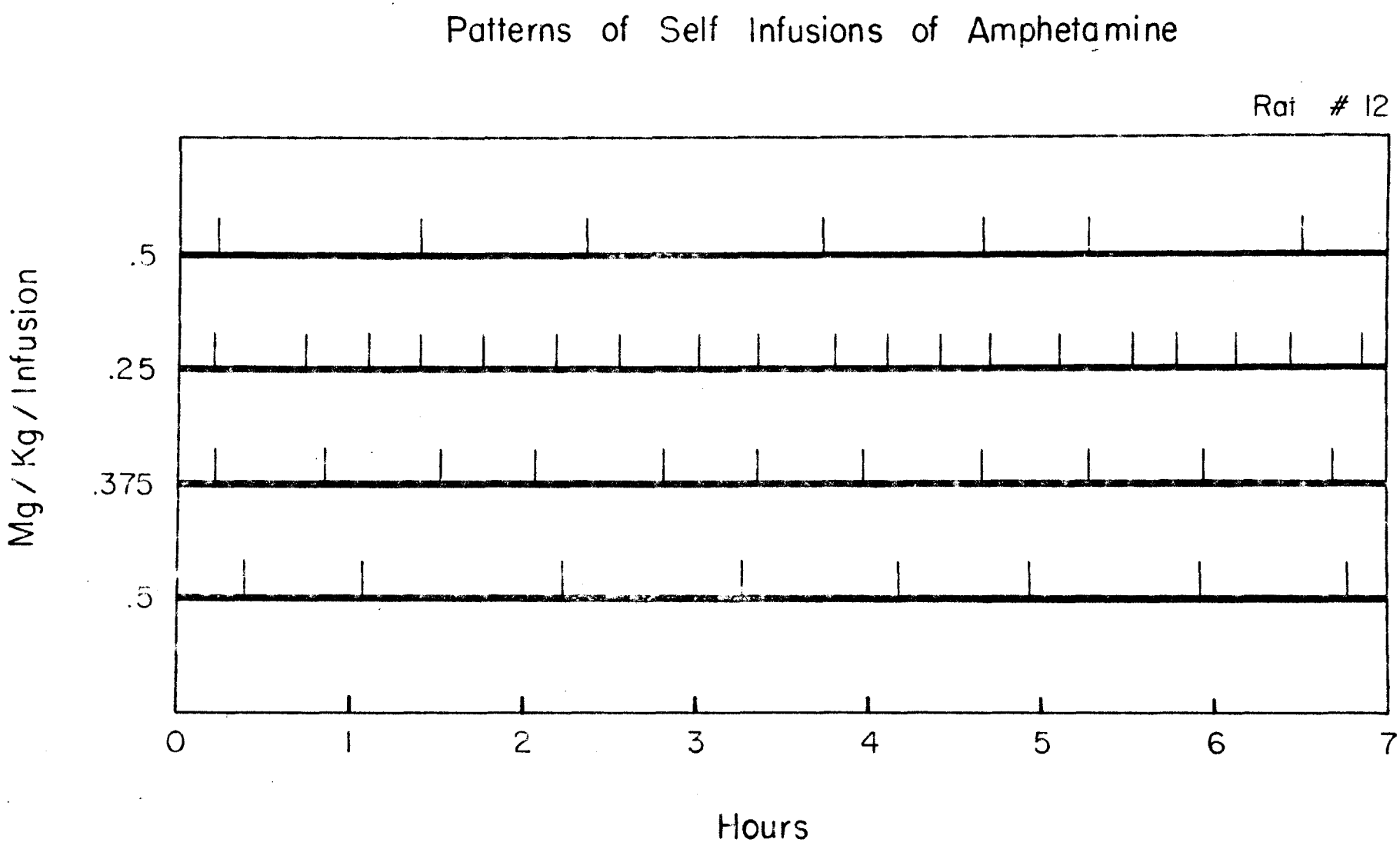

Rat #5
FR 1
1.0
.75
.5
.25
Mean Responses / Hour
.5
.75
1.0
Mg / Kg / Infusion
Amphetamine

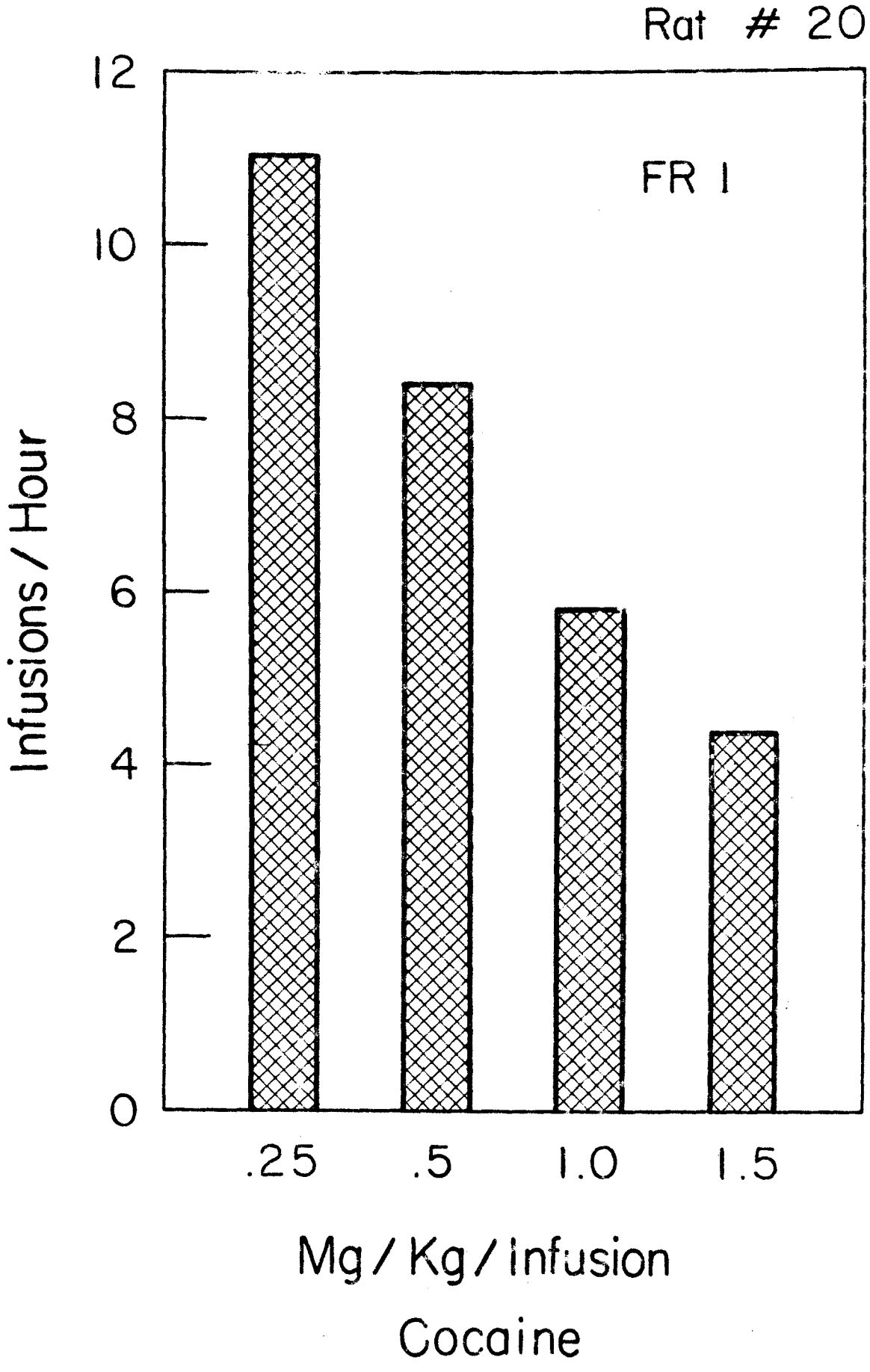

Patterns of Self Infusions of Amphetamine
Rat # 5
Mg / Kg / Infusion
.5
.75
1.0
0
1
2
3
4
5
6
7
8
Hours

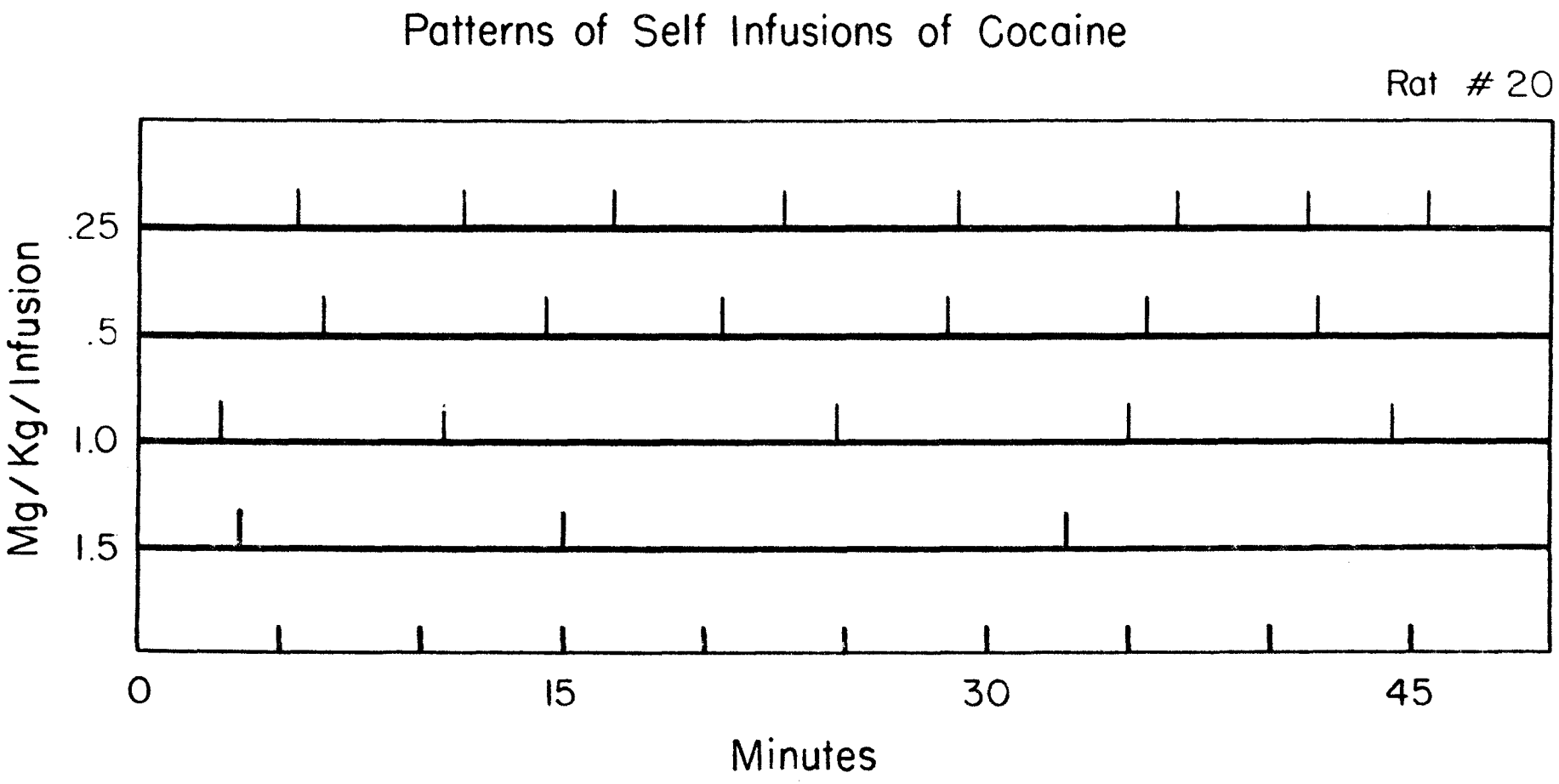

Rat # 7
FR 1
Mean Responses / Hour
2.5
2.0
1.5
1.0
.5
0
.25
.375
.5
Mg / Kg / Infusion
Amphetamine

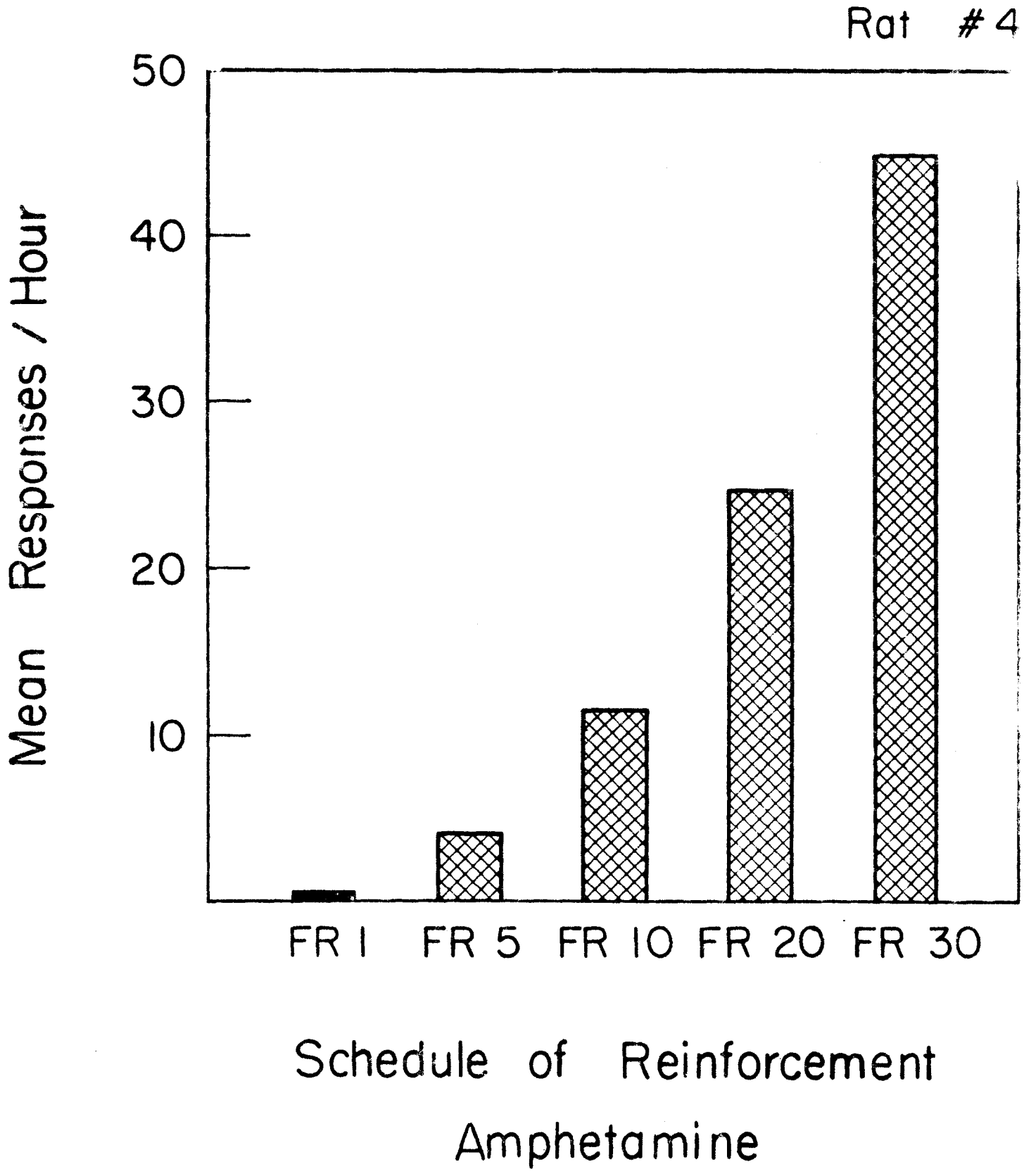

Patterns of Self Infusions of Amphetamine
Rat # 7
Mg / Kg / Infusion
.25
.375
.5
0
1
2
3
4
5
6
Hours

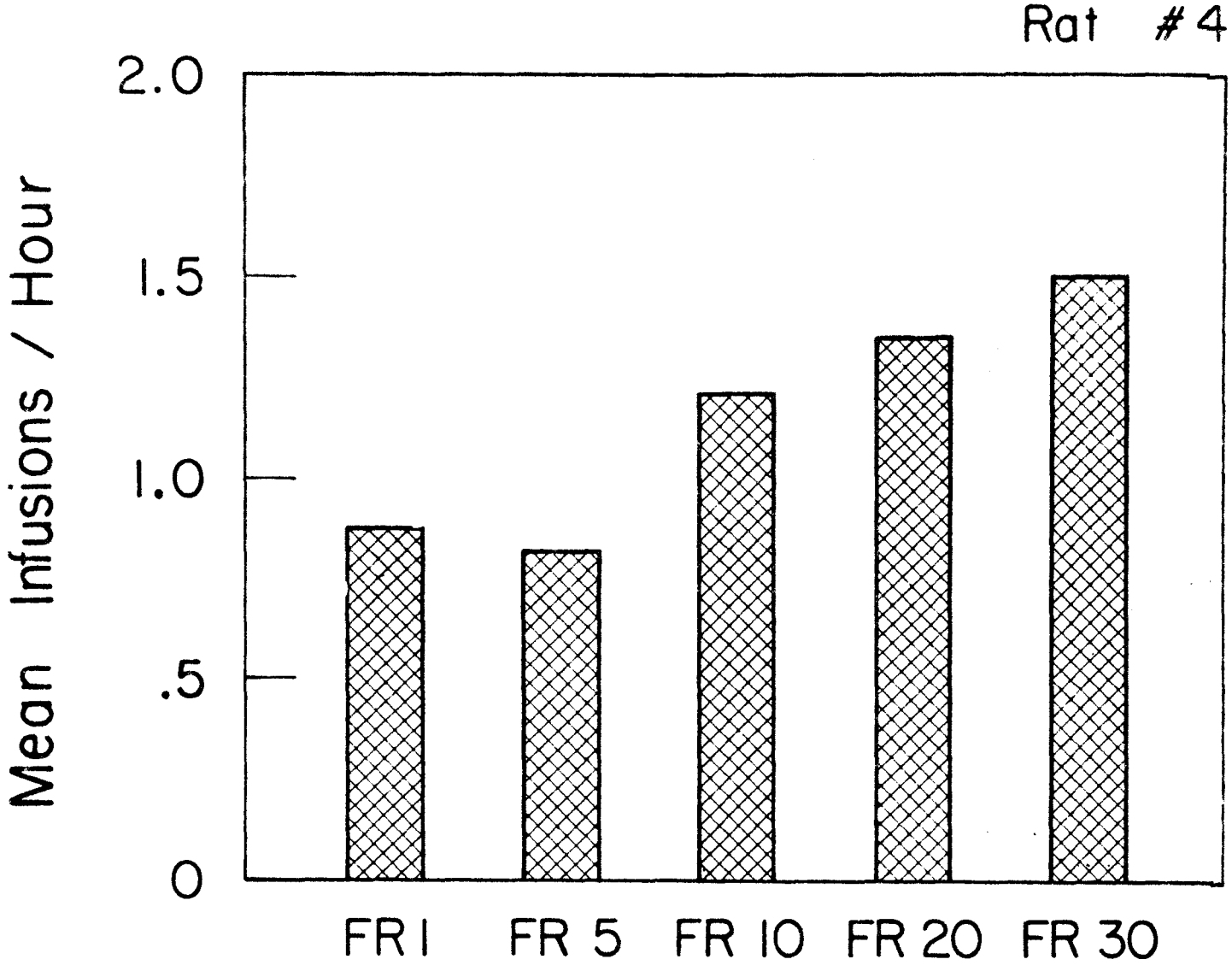

Rat # 12
FR 1
3.0
2.0
1.0
0
Mean Responses / Hour
.5
.375
.25
.5
Mg / Kg / Infusion
Amphetamine


Patterns of Self Infusions of Amphetamine
Rat # 12
Mg / Kg / Infusion
.5
.25
.375
.5
0
1
2
3
4
5
6
7
Hours


Rat # 20
FR 1
12
10
8
6
4
2
0
Infusions / Hour
.25
.5
1.0
1.5
Mg / Kg / Infusion
Cocaine


Patterns of Self Infusions of Cocaine
Rat # 20
Mg/Kg/Infusion
.25
.5
1.0
1.5
0
15
30
45
Minutes

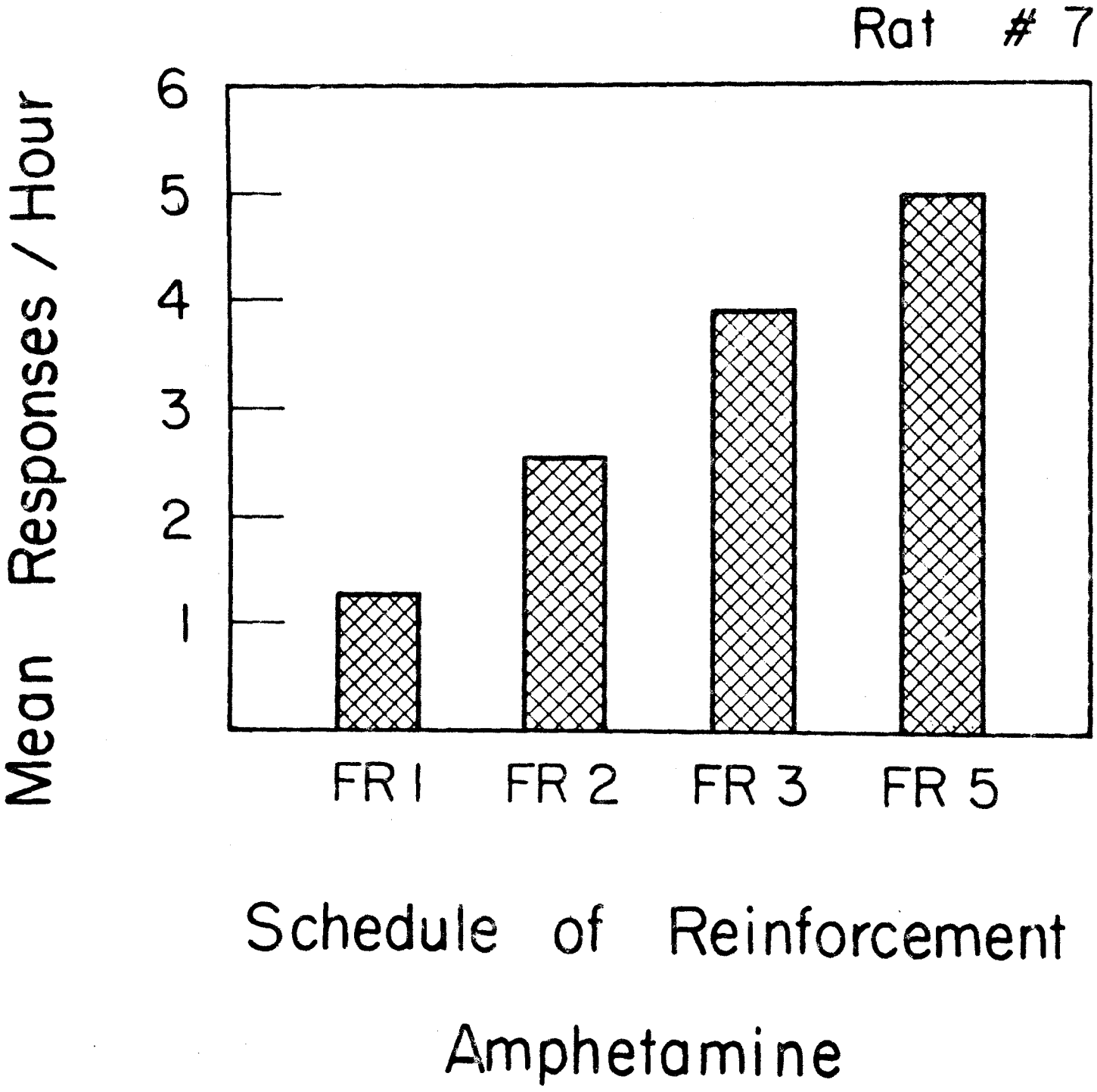

Rat #4
50
40
30
20
10
Mean Responses / Hour
FR 1
FR 5
FR 10
FR 20
FR 30
Schedule of Reinforcement
Amphetamine

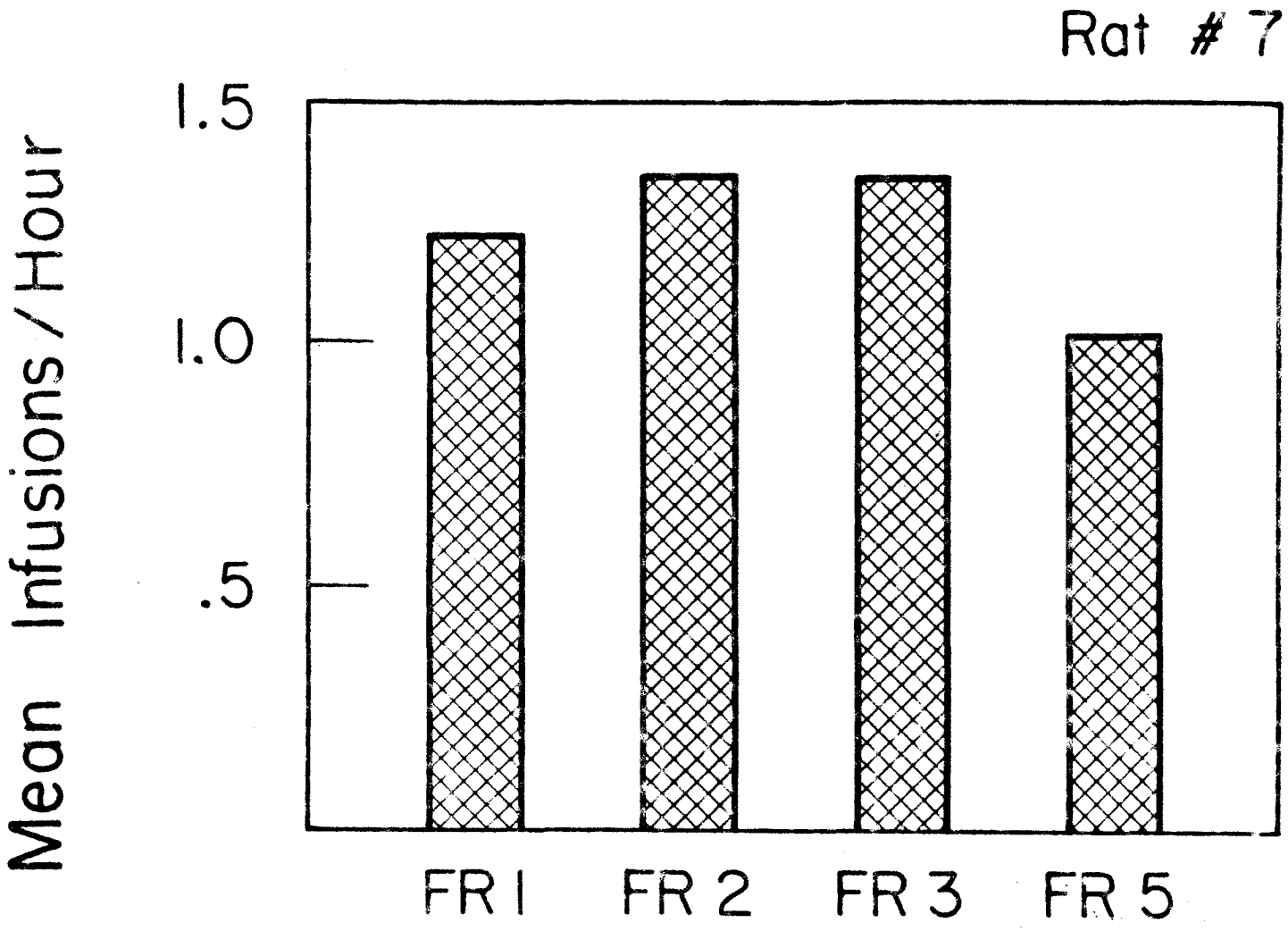


Schedule of Reinforcement

(.5 Mg/Kg/Infusion)

Amphetamine

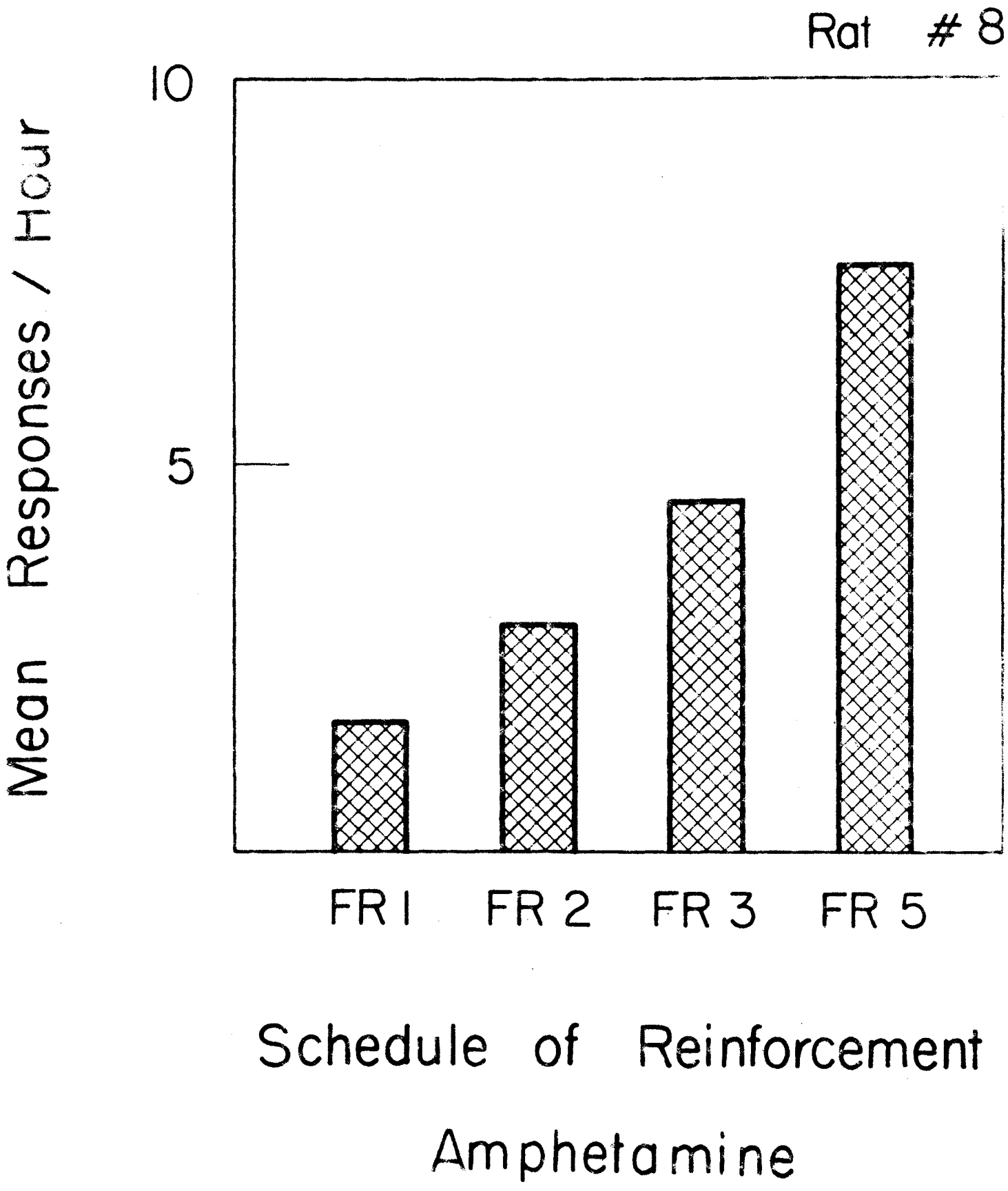

Rat # 7
Mean Responses / Hour
6
5
4
3
2
1
FR 1
FR 2
FR 3
FR 5
Schedule of Reinforcement
Amphetamine

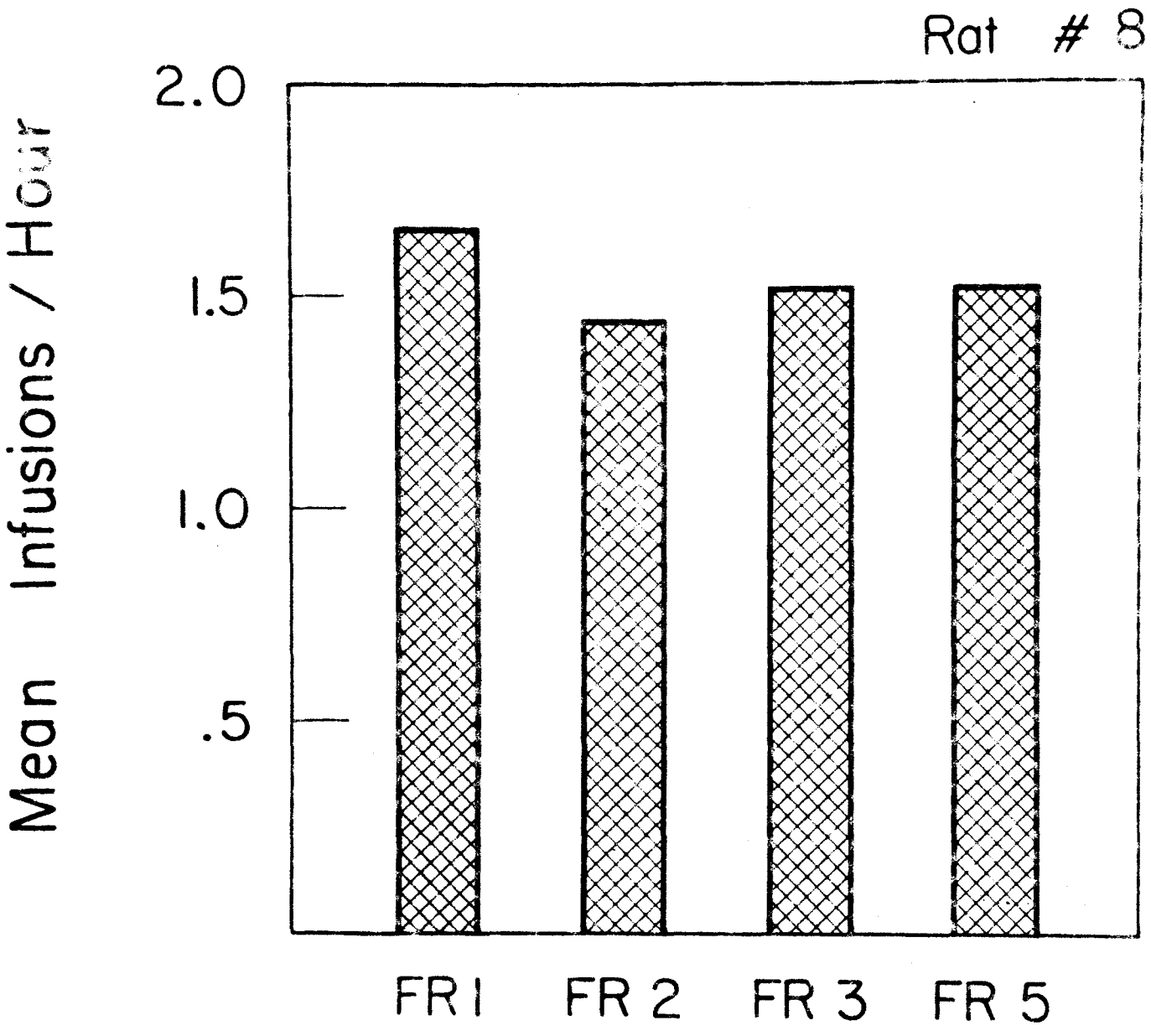


Schedule of Reinforcement

(.5 Mg/Kg/Infusion)

Amphetamine


Rat # 8
10
5
Mean Responses / Hour
FR 1
FR 2
FR 3
FR 5
Schedule of Reinforcement
Amphetamine


Rat # 8
2.0
1.5
1.0
.5
Mean Infusions / Hour
FR 1
FR 2
FR 3
FR 5
Schedule of Reinforcement
(.25 Mg/Kg/Infusion)
Amphetamine