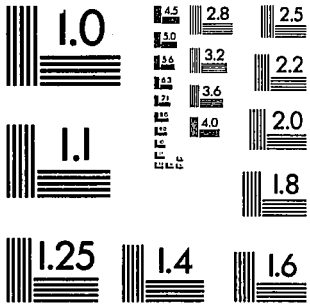
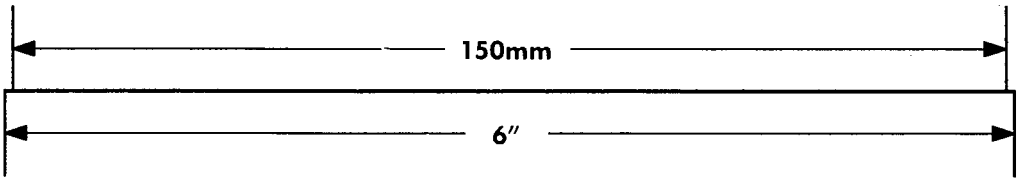
IMAGE EVALUATION TEST TARGET (MT-3)





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ADVANCES IN BEHAVIORAL PHARMACOLOGY, VOL. 2

Some Quantitative Behavioral Pharmacology in the Mouse

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I. INTRODUCTION

The mouse has long been used in the behavioral testing of pharmacological agents. The behavioral measures have ranged from observational to automated measurements of spontaneous motor activity (SMA). With the exception of some semi-quantitative studies on "conditioned avoidance responding" (CAR), there has been very little interest in the use of the mouse in the assessment of behavioral effects of drugs on conditioned behaviors such as schedule-controlled behavior. Schedule-controlled behavior has proven to be a valuable technique for the assessment of behavioral effects of pharmacological agents in other species.

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The behavior generated by schedules of reinforcement is objective, easily reproduced from laboratory to laboratory, stable from day to day, and sensitive to a wide variety of pharmacological agents.

A current difficulty in the use of schedule-controlled behavior in the mouse for behavioral assays is the relative paucity of published reports of drug effects on schedule-controlled behavior in the mouse. The lack of a large data base makes the interpretation of behavioral effects observed in a mouse after administration of a drug or toxic substance difficult and it is impossible to place the results into the context of the rest of behavioral pharmacology. There also is a suggestion from the existing behavioral literature in the mouse, mostly SMA, that the behavioral effects of a drug may be different in different genetic strains of mice. This has been reported most frequently for the effects of amphetamine and morphine.

The emergence of behavioral toxicology has prompted investigators to take a close look at the mouse for the behavioral assessment of toxic agents. The extensive use of the mouse in toxicology provides useful reference points, such as acute and chronic LD_{50}s with which to compare doses which produce behavioral effects. The likelihood that some animals will die, even in the behavioral testing of toxic substances, places some constraints on the type of animal a researcher is willing to risk. The low cost, the availability of pure genetic strains allowing subjects to be replaced by a very similar subject, and the use of training procedures which require a minimal amount of man-hours make the mouse a highly desirable species for behavioral toxicology. In addition, since some behavioral testing of toxic substances may require longitudinal studies with exposures at various ages, and testing at various times after exposures, it will be necessary to maintain a large animal colony. Thus, a species such as the mouse which can be housed in a small space, requires minimal care, and breeds easily under laboratory conditions, will be an excellent species with which to work.

If the mouse is to become an important species in future behavioral assays, it will become important to determine the nature of the reported strain differences. Second, it will become increasingly important that more quantitative behavioral assays, such as the use of schedule-controlled patterns of behavior, be adapted for use in the mouse, and a sufficient data base of drug effects on such behavior patterns must be developed to determine if significant differences exist between the mouse and other more widely studied species.

This chapter will attempt to compile the quantitative studies on the behavioral effects of drugs in the mouse with emphasis on strain differences in the response to drugs, the use of schedule-controlled behavior techniques in the mouse, and the effects of drugs on schedule-controlled behavior in the mouse. Since strain differences in the behavioral effects of drugs have been most widely studied on SMA, the effects of a few prototype drugs on SMA will be discussed before a detailed analysis of strain differences is presented.

II. EFFECTS OF DRUGS ON SMA

SMA can be described as the physical movement of the experimental subject. The variables which initiate the behavior, as well as the variables which control the amount of behavior emitted, are not understood. Hence, it has been called "spontaneous." SMA is recorded in a variety of ways: estimates of the duration of movement and the amount of movement can be recorded by an observer; the movement of a subject within a confined space can be recorded automatically by the subject interrupting photocell beams crossing the chamber in various configurations; movement can be recorded by placing the subject in a cage with a transverse central axis, and the movement of the subject activates microswitches placed at each end of the cage; the movement of the subject can be recorded by ultrasonic circuits in which movement of the subject alters standing waves within the chamber, and the alterations in reflected energy are recorded and converted to a digital output; the movement of a subject in a running wheel can be recorded by counting revolutions or partial revolutions of the wheel. (For a more detailed review of available techniques for recording SMA, see Finger, 1972.)

Despite the fact that SMA is influenced by many variables, for example, time of day, previous experience in the test chamber, amount of illumination in the test chamber, age, nutritional state, whether the mice are tested in groups or isolated, etc., the effects of drugs on SMA have been surprisingly consistent. (For recent review of the variables influencing SMA, see Robbins, 1977.)

Drugs which affect SMA are of two types: those drugs which increase SMA at low doses and decrease SMA at high doses, and those drugs which produce only decreases in SMA. Within the various pharmacological classes of drugs, there is good qualitative agreement in the effects measured on SMA. Changes in structure of the parent compound usually result only in quantitative changes in the effect on SMA. For this reason, only the effects of prototype drugs will be discussed in this section.

SMA is increased in the mouse following doses of amphetamine, atropine, caffeine, chlordiazepoxide, and morphine. As the dose of each drug is increased, a dose is reached which will decrease SMA. In contrast, chlorpromazine, ethanol, pentobarbital, and 1-Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC) are reported to produce only decreases in SMA in the mouse. Although these are the general findings, there are interesting reports of both qualitative and quantitative differences in the response to several drugs.

For example, *d*-amphetamine is generally reported to increase SMA over a dose range of approximately 3–300 μmoles/kg free base. At doses above 300 μmoles/kg, SMA is decreased. The increases observed in SMA, however, vary over quite a large range. Weissman (1972) reported a 27-fold increase over control levels of SMA in Swiss mice at a dose of 54 μmoles/kg *d*-amphetamine (10 mg/kg *d*-amphetamine sulfate). At a similar dose (59.2 μmoles/kg) of

d-amphetamine, Strömberg and Svensson (1975) reported only a 5-fold increase in the SMA of NMRI mice, and Anisman, Wahlsten, and Kokkinidis (1975) report an increase of 1.2 times the control level of SMA in C57BL mice at a dose of 54 μmoles/kg.

Morphine is another example. While it is generally reported that morphine increases SMA over a dose range of approximately 10–300 μmoles/kg, there are large differences reported. Kuschinsky (1974) reported a 15-fold increase in SMA in Swiss mice following a dose of 70 μmoles/kg morphine base (approximately 27 mg/kg morphine sulfate), while at the same dose, Castellano, Llovera, and Oliverio (1975) report essentially no effect on SMA in DBA mice.

Although not as extensively studied, quantitative differences have been reported for atropine. Waldeck (1974) reported increases in SMA in NMRI mice following doses above 40 μmoles/kg atropine base (approximately 14 mg/kg atropine sulfate), while Ahtee and Shillito (1970) report no effect at doses up to 58 μmoles/kg in albino mice.

In contrast, the effects of caffeine and chlordiazepoxide are fairly consistent. Increases in SMA are reported over a dose range of 13–100 μmoles/kg (2.5–20 mg/kg) caffeine (Dews, 1953; Waldeck, 1975). Doses above 100 μmoles/kg are generally reported to decrease SMA; however, Estler (1973) reported an increase in SMA following a dose of 208 μmoles/kg. Chlordiazepoxide produces small increases (less than 2-fold) in SMA over a dose range of 20–100 μmoles/kg (6–32 mg/kg chlordiazepoxide·HCl). Lower doses are without effect, and higher doses decrease SMA (Ahtee & Shillito, 1970; Minck, Danneberg, & Knappen, 1974; Sethy, Naik, & Sheth, 1970; Zwirner, Porsolt, & Loew, 1975).

Among the drugs reported to only decrease SMA in mice, the effects of chlorpromizine and Δ^9-THC are fairly consistent. Chlorpromazine decreases SMA at doses above 7 μmoles/kg (approximately 2.3 mg/kg chlorpromazine·HCl), with lower doses having no effect (Berger, 1969; Buckley, Steenberg, Barry, & Manian, 1973; Fuller, 1966; M. E. Goldberg, Dubnick, Hefner, & Salama, 1973; Kršiak & Janků, 1971; Minck *et al.*, 1974; Sethy *et al.*, 1970; Zwirner *et al.*, 1975). Similarly, Δ^9-THC is reported to decrease SMA at doses above 15 μmoles/kg (approximately 4.7 mg/kg), with lower doses having no effect (P. F. Anderson, Jackson, Chesher, & Malor, 1975; Brown, 1972).

Holtzman and Schneider (1974), and Randall, Carpenter, Lester, and Friedman (1975) reported that ethanol decreased SMA in C57BL and CF-1 mice at doses above 2 mmoles/kg (100 mg/kg). However, Randall *et al.* (1975) reported an increase in SMA in BALB/c mice over a dose range of 16–49 mmoles/kg. There are similar differences reported for pentobarbital. At doses above 40 μmoles/kg (10 mg/kg Na·pentobarbital), SMA is decreased in OF-1, CF-1, and albino mice (Brown, 1972; Sethy *et al.*, 1970; Zwirner *et al.*, 1975). However, Waldeck (1975) reported 2- to 3-fold increases in SMA in NMRI mice over a dose range of 32–129 μmoles/kg.

Thus, the suggestion is that where differences exist in the reported effects of drugs on SMA, the difference can be attributed to a difference among the strains. Since a true genetic difference in the pharmacological activity of a drug would be likely to affect results on a wide variety of behavioral measures and not just SMA, a more detailed analysis of the reported differences is warranted.

III. STRAIN DIFFERENCES IN THE EFFECTS OF DRUGS ON SMA

As noted previously, there is a suggestion in the literature on SMA that the different genetic strains of mice respond differently to drugs. These effects have been most widely studied for amphetamine and morphine, both of which increase SMA in mice. The differences among strains in response to amphetamine and morphine will now be examined in some detail from existing reports in the literature.

When dealing with effects of drugs on SMA, it is necessary to study a broad range of doses. This is especially important when a comparison is being made between species which may have different quantitative, as well as qualitative, responses to a drug. The reason for this is exemplified by amphetamine. At low doses, amphetamine increases SMA in most species. However, as higher and higher doses are studied, a dose will be reached at which the maximum drug effect is achieved. At doses above the maximally effective dose, the increases due to amphetamine will become smaller. Eventually, a dose will be reached which will decrease SMA below the control value. The shape of the dose-effect curve can be described as biphasic. When attempting to compare the effects of amphetamine, or any drug, from published reports on different strains, it is necessary to know the effect of at least two doses in order to determine if the doses are on the ascending or the descending limb of the dose-effect curve. Thus, reports on the effects of a single dose of amphetamine could not be used in the following comparison between strains.

In order to determine if the reported differences in the effects of drugs on SMA in the different strains could be attributed to differences in the control behavior, it was necessary to know the control value of SMA. Therefore, results published only as ratios without the absolute value for control or results published as *F* values could not be used.

There were other problems encountered reviewing the literature which were decided on an individual basis. For example, when a strain of mice is reported as "white" or "albino," does this mean BALB/c or Swiss? The drug effects reported using white or albino mice were not statistically different from the drug effects reported using the Swiss strain of mice. Thus, the white or albino studies were included in the data for the Swiss strain. They are identified, however, in

Tables I and II. A second example of a common problem is the lack of information of the dosage form. Many papers do not include the salt of amphetamine used, or whether the salt or free base was used to calculate the doses given. Since this did vary considerably from paper to paper where stated, a standardized dose form has been used. All doses of *d*-amphetamine and morphine are expressed in μmoles/kg of amphetamine and morphine base. The route of administration has been overwhelmingly either intraperitoneal or subcutaneous, and thus since the data have been pooled over as much as one-half a log unit for most comparisons, the route of administration has been ignored. Treatment times in the literature are quite varied, as well as the total time of observation following drug administration. In making comparisons of this nature, one has no choice but to accept the results as published and a decision to reject a study, *post hoc*, cannot be made, because a treatment time was wrong, etc. However, again the pooling of data over one-half log unit increments helps reduce this source of variation. Finally, in making comparisons among published reports there will be errors made in reading values from published graphs; that is, two people looking at the same graph may not arrive at exactly the same value for a particular point. However, since all the data were collected from the literature before any pooling or graphing was attempted, the possibility of introducing a subjective bias was greatly reduced. An apology is rendered to those authors whose data have been misunderstood or mishandled.

A. Effects of *d*-Amphetamine on SMA in Different Strains

Table I summarizes the reported effects of amphetamine on SMA in the four most frequently studied strains: Swiss, NMRI, CF-1, and C57BL. To compare the strains, the effects of amphetamine over a one-half log unit range of doses have been averaged and plotted for each of the four strains in Fig. 1. Ignoring the variation in each of the points plotted, the differences in method in the separate studies cited, the number of animals used, and the differences in the time over which the effects were measured, it is apparent from Fig. 1 that differences do exist among the four strains in their response to amphetamine. The increase in SMA observed in the Swiss strain following doses in the 30–100 μmole/kg range is some 6-fold greater than the increase observed when the C57BL strain is used. The NMRI and CF-1 strains appear to be relatively similar, and are approximately halfway between the Swiss and C57BL strains. There is, thus, evidence of quantitative differences in the effects of amphetamine on SMA in different strains of mice.

In a recent review by Dews and Wenger (1977), the effects of amphetamine in a wide variety of species upon a wide variety of behaviors were examined and shown to be dependent on the control rate of responding or the rate of ongoing behavior. This relationship was shown to apply to SMA as well as to schedule-

TABLE I
EFFECTS OF *d*-AMPHETAMINE ON SMA IN FOUR STRAINS OF MICE

Dose[a] (μmoles/kg)	Control rate[b]	Drug/Control[c]	Method[d]	Strain	Reference
			0.31–1.0 μmoles/kg		
0.54	0.001	2.7	PC	Swiss	Weissman (1972)
Mean		2.7			
			1.1–3.0 μmoles/kg		
1.6	0.001	1.9	PC	Swiss	Weissman (1972)
2.7	0.12	1.2	PC	Albino	Thornburg & Moore (1972)
Mean		1.55			
			3.1–10.0 μmoles/kg		
3.7	1.02	1.5	PC	Swiss	Maickel, Levine, & Quirce (1974)
5.4	0.001	2.7	PC	Swiss	Weissman (1972)
5.4	0.02	2.9	PC	Swiss	Rethy, Smith, & Villarreal (1971)
5.4	0.12	2.0	PC	Albino	Thornburg & Moore (1972)
5.4	0.17	0.8	PC	Swiss	Smith (1963)
5.4	0.41	3.0	PC	Albino	Thornburg & Moore (1973)
7.4	1.02	2.4	PC	Swiss	Maickel, Levine, & Quirce (1974)
Mean		2.19			
			10.1–30.0 μmoles/kg		
10.8	0.12	6.5	PC	Albino	Thornburg & Moore (1972)
10.8	0.41	3.9	PC	Albino	Thornburg & Moore (1973)
13.5	0.18	1.9	PC	Swiss	Maj, Sowinska, Kapturkiewicz, & Surnek (1972)
14.8	1.02	3.1	PC	Swiss	Maickel, Levine, & Quirce (1974)
16.2	0.02	6.4	PC	Swiss	Rethy, Smith, & Villarreal (1971)
16.2	0.08	2.6	Br. Pl.	White	Galambos, Pfeifer, György, & Molnar (1967)
16.2	0.17	1.3	PC	Swiss	Smith (1963)
17.3	0.001	18.6	PC	Swiss	Weissman (1972)
21.6	0.12	13.9	PC	Albino	Thornburg & Moore (1972)
21.6	0.41	5.7	PC	Albino	Thornburg & Moore (1973)
27.0	0.08	4.2	Br. Pl.	White	Galmbos, Pfeifer, György, & Molnar (1967)
27.0	0.18	3.4	PC	Swiss	Maj, Sowinska, Kapturkiewicz, & Surnek (1972)
29.6	1.02	2.8	PC	Swiss	Maickel, Levine, & Quirce (1974)
Mean		5.72			

(continued)

TABLE I—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
			30.1–100 μmoles/kg		
43.2	0.12	11.3	PC	Albino	Thornburg & Moore (1972)
54	0.001	27.1	PC	Swiss	Weissman (1972)
54	0.02	5.5	PC	Swiss	Rethy, Smith, & Villarreal (1971)
54	0.17	2.0	PC	Swiss	Smith (1963)
59.2	1.02	2.4	PC	Swiss	Maickel, Levine, & Quirce (1974)
64.8	0.12	4.4	PC	Albino	Thornburg & Moore (1972)
Mean		8.78			
			100.1–300 μmoles/kg		
162	0.02	1.33	PC	Swiss	Rethy, Smith, & Villarreal (1971)
162	0.17	1.08	PC	Swiss	Smith (1963)
172.8	0.001	15.3	PC	Swiss	Weissman (1972)
Mean		5.90			
			301–1000 μmoles/kg		
540	0.17	0.75	PC	Swiss	Smith (1963)
Mean		0.75			
			0.1–0.3 μmoles/kg		
0.2	0.11	1.0	PC	NMRI	Strömburg & Svensson (1975)
Mean		1.0			
			0.31–1.0 μmoles/kg		
0.4	0.11	1.0	PC	NMRI	Strömburg & Svensson (1975)
0.96	0.11	1.1	PC	NMRI	Strömburg & Svensson (1975)
Mean		1.05			
			1.1–3.0 μmoles/kg		
1.9	0.11	1.0	PC	NMRI	Strömburg & Svensson (1975)
			3.1–10.0 μmoles/kg		
3.7	0.11	1.5	PC	NMRI	Strömburg & Svensson (1975)
4.7	0.19	0.9	Obs:quad.cr.	NMRI	Minck, Danneberg, & Knappen (1974)
7.4	0.11	2.2	PC	NMRI	Strömburg & Svensson (1975)
9.3	0.19	1.0	Obs:quad.cr.	NMRI	Minck, Danneberg, & Knappen (1974)
Mean		1.4			

TABLE I—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	Reference
			10.1–30 μmoles/kg		
14.8	0.11	3.3	PC	NMRI	Strömburg & Svensson (1975)
18.5	0.19	1.0	Obs:quad.cr.	NMRI	Minck, Danneberg, & Knappen (1974)
18.5	1.25	1.9	Animex act.	NMRI	Svensson (1971)
29.6	0.11	4.3	PC	NMRI	Strömburg & Svensson (1975)
Mean		2.63			
			30.1–100 μmoles/kg		
37	0.19	1.3	Obs:quad.cr.	NMRI	Minck, Danneberg, & Knappen (1974)
59.2	0.11	5.3	PC	NMRI	Strömburg & Svensson (1975)
74	0.19	2.4	Obs:quad.cr.	NMRI	Minck, Danneberg, & Knappen (1974)
74	1.25	1.9	Animex act.	NMRI	Svensson (1971)
Mean		2.73			
			101–300 μmoles/kg		
118.4	0.11	4.0	PC	NMRI	Strömburg & Svensson (1975)
236.8	0.11	2.3	PC	NMRI	Strömburg & Svensson (1975)
Mean		3.15			
			1.1–3.0 μmoles/kg		
2.7	0.84	1.1	PC	CF-1	Glick & Marsanico (1974)
Mean		1.1			
			3.1–10.0 μmoles/kg		
4.6	0.13	1.7	PC	CF-1	Dews (1953)
5.4	0.07	1.0	PC	CF-1	Holtzman (1974)
9.3	0.13	1.3	PC	CF-1	Dews (1953)
Mean		1.33			
			10.1–30 μmoles/kg		
10.8	0.84	1.6	PC	CF-1	Glick & Marsanico (1974)
16.2	0.07	1.8	PC	CF-1	Holtzman (1974)
18.5	0.13	1.6	PC	CF-1	Dews (1953)
22.2	0.01	7.5	PC	CF-1	Hitzemann, Loh, Craves, & Domino (1973)
Mean		3.13			
			30.1–100 μmoles/kg		
37	0.13	2.7	PC	CF-1	Dews (1953)
43.2	0.84	1.4	PC	CF-1	Glick & Marsanico (1974)

(continued)

TABLE I—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
54	0.07	5.7	PC	CF-1	Holtzman (1974)
74	0.01	9.0	PC	CF-1	Hitzemann, Loh, Craves, & Domino (1973)
74	0.13	3.1	PC	CF-1	Dews (1953)
86.4	0.84	1.2	PC	CF-1	Glick & Marsanico (1974)
Mean		3.85			
			101–300 μmoles/kg		
148	0.13	2.3	PC	CF-1	Dews (1953)
162	0.07	2.2	PC	CF-1	Holtzmann (1974)
222	0.01	5.0	PC	CF-1	Hitzemann, Loh, Craves, & Domino (1973)
296	0.13	0.9	PC	CF-1	Dews (1953)
Mean		2.6			
			301–1000 μmoles/kg		
540	0.07	1.0	PC	CF-1	Holtzman (1974)
592	0.13	0.3	PC	CF-1	Dews (1953)
Mean		0.65			
			1.1–3.0 μmoles/kg		
2.7	0.05	1.1	Fl.cr.:tilt	C57BL	Oliverio, Eleftheriou, & Bailey (1973)
Mean		1.1			
			3.1–10 μmoles/kg		
5.4	0.05	1.4	Fl.cr.:tilt	C57BL	Oliverio, Eleftheriou, & Bailey (1973)
5.4	0.37	0.9	Obs:quad.cr.	C57BL	Anisman, Wahlsten, & Kokkinidis (1975)
5.4	0.43	1.2	Obs:quad.cr.	C57BL	Anisman & Cygan (1975)
Mean		1.17			
			10.1–30 μmoles/kg		
10.8	0.05	1.6	Fl.cr.:tilt	C57BL	Oliverio, Eleftheriou, & Bailey (1973)
16.2	0.37	1.1	Obs:quad.cr.	C57BL	Anisman, Wahlsten, & Kokkinidis (1975)
27	0.37	1.3	Obs:quad.cr.	C57BL	Anisman, Wahlsten, & Kokkinidis (1975)
27	0.43	1.6	Obs:quad.cr.	C57BL	Anisman & Cygan (1975)
Mean		1.40			

TABLE I—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
			30.1–100 μmoles/kg		
54	0.37	1.2	Obs:quad.cr.	C57BL	Anisman, Wahlsten, & Kokkinidis (1975)
54	0.43	1.5	Obs:quad.cr.	C57BL	Anisman & Cygan (1975)
Mean		1.4			

[a]Dose (μmoles/kg): the amount of free base administered expressed in μmoles/kg.

[b]Control rate: the level of SMA in recorded units of activity per sec under control conditions. The recorded unit of activity depended on the method used to determine SMA, such as an interruption of a photocell beam as in Weissman (1972); or the completion of an electronic circuit when the mouse bridges between two conductive plates on the floor of the test chamber as in Galambos, Pfeifer, György, & Molnar (1967).

[c]Drug/control: the effect of a drug is defined as the rate of SMA following drug administration divided by the rate of SMA under control conditions.

[d]Method: the method used to determine the recorded units or the level of SMA.

Abbreviations: PC = the interruptions of a beam of light striking a photocell as in Weissman (1972); Br.Pl. = the mouse completes an electronic circuit by bridging between two conductive plates on the floor of the test chamber as in Galambos, Pfeifer, György, & Molnar (1967); Obs:quad.cr. = the mouse crosses a clearly marked line on the floor of the test chamber, dividing the floor into easily defined quadrants. The recording is done by an observer as in Minck, Danneberg, & Knappen (1974); Animex act. = the counts of SMA as determined by an Animex activity cage as in Svensson (1971); Fl.cr.:tilt = the mouse crosses the width of the test chamber causing the chamber to tilt on a central axis operating a microswitch as in Oliverio, Eleftheriou, & Bailey (1973).

controlled behavior. The question, therefore, arises as to whether the differences between strains relate to differences in control SMA of the different strains, with the appropriate amphetamine effect for the given control level of SMA; or whether the differences are actually due to some other factor, such as receptor affinity or metabolism? If the differences in effects are due to differences in the control level of SMA, then altering the level of SMA in a given strain would produce a different effect. For example, if a mouse is put in a test chamber, it initially has a high level of SMA which gradually decreases with time. If amphetamine was given to one group of mice immediately prior to the introduction to the test chamber, a different effect would be observed compared with controls than if amphetamine would be given to mice of the same strain after having been in the test chamber for 1 hr. In this case, the measured effect would be different, but the physiological responses to amphetamine would not be different.

To attempt to answer this question, the effects of amphetamine in the four most frequently used strains were replotted as a function of the control rate of SMA in a manner similar to that reported by Dews (1964) and Dews and Wenger (1977). In order to obtain enough data points to make a comparison among the

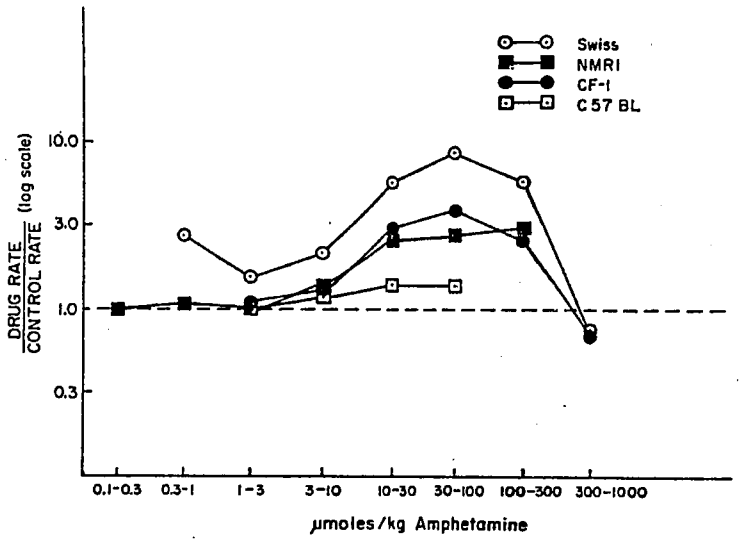

Fig. 1. The mean effect of *d*-amphetamine on SMA in four strains of mice (data from Table I). Abscissa: dose in μmoles/kg of body weight, pooled over one-half log unit ranges; ordinate: ratio of the rate of SMA following drug administration to the rate of SMA under control conditions; 5.4 μmoles/kg amphetamine base = 1 mg/kg amphetamine·SO_4.

strains, the effects reported following a range of doses (10–56 μmoles/kg) were plotted (Fig. 2). It can be seen that there is a considerable overlap among three of the four strains, and a single regression line ($y = -0.35x + 0.17$) can be derived, which is a pretty good fit for all points. This suggests that the differences among at least three of the four strains in the response to amphetamine seen in Fig. 2 may be related to quantitative differences in rate rather than genetically determined difference in the physiological response to amphetamine. The points plotted for the C57BL strain do not appear to be as well scattered along the regression line as do the points for the other three strains. In fact, all the points for the C57BL strain lie below the line.

Although Fig. 2 is suggestive of the importance of the control rate in the strain differences reported for amphetamine, the wide dose range and difference among the studies used to obtain the points in the figure contribute to the scatter, and the relationship to control rates may be stronger than observed. To examine this possibility more closely, a single study in which at least three strains were studied using the same doses and methods is desirable. Fortunately, two studies were found from the same laboratory which each used the same methods, doses, and three strains. Each strain had a slightly different rate providing six different

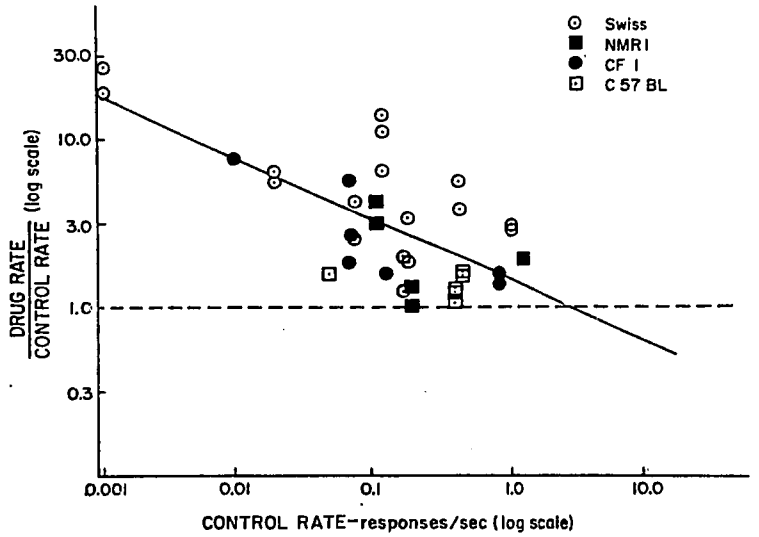

Fig. 2. The dependence of the effect of *d*-amphetamine on the control rate of SMA in four strains of mice over a dose range of 10.0-56.0 μmoles/kg (data from Table I). Abscissa: control rate of SMA (log scale); ordinate: the ratio of the rate of SMA following drug administration to the rate of SMA under control conditions (log scale). The regression line was calculated by the method of least squares: $y = -0.35x + 0.17$.

control rates. The data from the two studies (Anisman & Cygan, 1975; Anisman *et al.*, 1975) are replotted in Fig. 3 as the total activity counts per 15 min. There are clear differences among the strains, but the differences suggest a rate-dependent effect.

If the data are replotted in a manner similar to Fig. 2, the result is quite clear (Fig. 4). The difference among the three strains in response to a given dose of amphetamine is a function of the control rate of activity. As the dose is increased, the slope of the regression line becomes more negative (27 μmoles/kg: $y = -0.4x + 0.06$; 54 μmoles/kg: $y = -0.85x - 0.2$). The negative slope observed with increasing doses is in agreement with the general trend observed from the pooled data plotted in Fig. 2 and supports the conclusion that differences in the level of activity can account for some reported strain differences to amphetamine in mice. There may be an additional factor responsible for the difference between the C57BL strain and the Swiss, NMRI, and CF-1 strains, but the control level of SMA seems to account for the differences between the C57BL/6J, DBA/2J, and A/J strains.

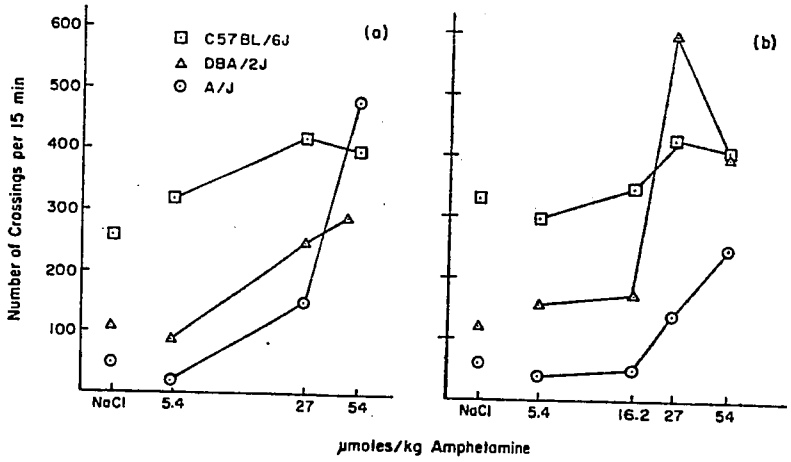

Fig. 3. The effect of *d*-amphetamine on SMA in three strains of mice. Replotted from Anisman and Cygan, 1975(a), and Anisman, Wahlsten, and Kokkinidis, 1975(b). Abscissa: dose in μmoles/kg of body weight on a log scale; ordinate: level of SMA plotted as the number of observed quadrant crossings per 15 min. Points at NaCl represent data obtained after saline administration.

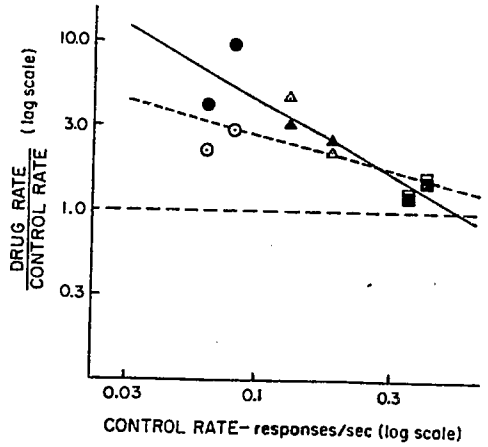

Fig. 4. The dependence of the effect of *d*-amphetamine on the control rate of SMA in three strains of mice. (Replotted from Anisman & Cygan (1975); Anisman, Wahlsten, & Kokkinidis, 1975.) Data plotted as in Fig. 2. Regression lines were fitted by the method of least squares. 27 μmoles/kg: $y = -0.4x + 0.06$; 54 μmoles/kg: $y = -0.85x - 0.2$. Circles, A/J strain; triangles, DBA/2J strain; rectangles, C57BL/6J strain. Open symbols and broken line represent the effect of 27 μmoles/kg; closed symbols and solid line represent the effect of 54 μmoles/kg.

B. Effects of Morphine on SMA in Different Strains

Table II summarizes the reported effects of morphine on SMA in the four most frequently studied strains: Swiss, C57BL, BALB/c, and DBA. As with amphetamine, the effect of morphine in each strain has been pooled over a one-half log unit range of doses, and the mean effect for each strain is plotted in Fig. 5. Again, there are marked differences among the four strains. SMA is increased the most in Swiss mice, and activity is unchanged at the doses studied in mice of the DBA strain. At the 30–100 μmole/kg dose range, this difference is 8-fold. The C57BL and BALB/c mice seem to be somewhat more similar, the effect of morphine being between that observed in Swiss and DBA mice.

TABLE II
EFFECTS OF MORPHINE ON SMA IN FOUR STRAINS OF MICE

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
			10–30 μmoles/kg		
17.5	0.10	3.9	Animex act.	Albino	Kuschinsky (1974)
26	0.02	1.7	PC	Swiss	Rethy, Smith, & Villarreal (1971)
26	0.75	0.3	Run.wh.[a]	Swiss	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
Mean		2.0			
			30.1–100 μmoles/kg		
35	0.10	4.7	Animex act.	Albino	Kuschinsky (1974)
52	0.75	0.2	Run.wh.	Swiss	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
53.2	0.23	1.0	PC	White	Mattila & Saarnivaara (1967)
70	0.10	15.0	Animex act.	Albino	Kuschinsky (1974)
78	0.02	10.8	PC	Swiss	Rethy, Smith, & Villarreal (1971)
Mean		6.3			
			100.1–300 μmoles/kg		
104	0.75	1.3	Run.wh.	Swiss	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
106.4	0.23	1.4	PC	White	Mattila & Saarnivaara (1967)
140	0.10	17.8	Animex act.	Albino	Kuschinsky (1974)
208	0.75	1.3	Run.wh.	Swiss	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
260	0.02	15.8	PC	Swiss	Rethy, Smith, & Villarreal (1971)
Mean		7.5			

(continued)

TABLE II—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
			300.1–1000 μmoles/kg		
780	0.02	7.5	PC	Swiss	Rethy, Smith, & Villarreal (1971)
Mean		7.5			
			10–30 μmoles/kg		
13	0.04	1.7	Fl.cr.:tilt	C57BL	Oliverio & Castellano (1974)
13.3	0.04	1.5	Fl.cr.:tilt	C57BL	Castellano & Oliverio (1975)
17.5	0.04	1.6	Fl.cr.:tilt	C57BL	Castellano, Llovera, & Oliverio (1975)
26	0.04	3.5	Fl.cr.:tilt	C57BL	Oliverio & Castellano (1974)
26	1.17	0.4	Run.wh.	C57BL	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
26.6	0.04	3.3	Fl.cr.:tilt	C57BL	Castellano & Oliverio (1975)
26.6	0.04	3.4	Fl.cr.:tilt	C57BL	Oliverio, Castellano, & Eleftheriou (1975)
Mean		2.2			
			30.1–100 μmoles/kg		
32.5	0.09	2.5	PC	C57BL	Shuster, Webster, Yu, & Eleftheriou (1975)
35	0.04	3.2	Fl.cr.:tilt	C57BL	Castellano, Llovera, & Oliverio (1975)
52	0.04	4.3	Fl.cr.:tilt	C57BL	Oliverio & Castellano (1974)
52	1.17	1.1	Run.wh.	C57BL	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
53.2	0.04	4.1	Fl.cr.:tilt	C57BL	Castellano & Oliverio (1975)
53.2	0.04	3.7	Fl.cr.:tilt	C57BL	Oliverio, Castellano, & Eleftheriou (1975)
65	0.09	4.4	PC	C57BL	Shuster, Webster, Yu, & Eleftheriou (1975)
70	0.04	4.3	Fl.cr.:tilt	C57BL	Castellano, Llovera, & Oliverio (1975)
Mean		3.5			
			100.1–300 μmoles/kg		
104	0.08	3.7	PC	C57BL	Shuster, Webster, Yu, & Eleftheriou (1975)
104	1.17	1.2	Run.wh.	C57BL	Eidelberg, Ersparmer, Kreinick, & Harris (1975)

TABLE II—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
208	1.17	1.0	Run.wh.	C57BL	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
Mean		2.0			
			10–30 μmoles/kg		
13	0.03	1.3	Fl.cr.:tilt	BALB/c	Oliverio & Castellano (1974)
13.3	0.03	1.3	Fl.cr.:tilt	BALB/c	Castellano & Oliverio (1975)
26	0.03	2.0	Fl.cr.:tilt	BALB/c	Oliverio & Castellano (1974)
26	0.48	0.3	Run.wh.	BALB/c	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
26.6	0.03	1.8	Fl.cr.:tilt	BALB/c	Castellano & Oliverio (1975)
26.6	0.03	2.4	Fl.cr.:tilt	BALB/c	Oliverio, Castellano, & Eleftheriou (1975)
Mean		1.5			
			30.1–100 μmoles/kg		
32.5	0.11	1.9	PC	BALB/c	Shuster, Webster, Yu, & Eleftheriou (1975)
52	0.03	2.5	Fl.cr.:tilt	BALB/c	Oliverio & Castellano (1974)
52	0.48	1.0	Run.wh.	BALB/c	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
53.2	0.03	2.2	Fl.cr.:tilt	BALB/c	Castellano & Oliverio (1975)
53.2	0.03	2.8	Fl.cr.:tilt	BALB/c	Oliverio, Castellano, & Eleftheriou (1975)
65	0.08	1.1	PC	BALB/c	Shuster, Webster, Yu, & Eleftheriou (1975)
Mean		1.9			
			100.1–300 μmoles/kg		
104	0.11	1.9	PC	BALB/c	Shuster, Webster, Yu, & Eleftheriou (1975)
104	0.48	2.3	Run.wh.	BALB/c	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
208	0.48	2.3	Run.wh.	BALB/c	Eidelberg, Ersparmer, Kreinick, & Harris (1975)
Mean		2.2			
			10–30 μmoles/kg		
13.3	0.03	0.8	Fl.cr.:tilt	DBA	Castellano & Oliverio (1975)
13.3	0.03	1.1	Fl.cr.:tilt	DBA	Oliverio & Castellano (1974)
17.5	0.03	1.0	Fl.cr.:tilt	DBA	Castellano, Llovera, & Oliverio (1975)

(continued)

TABLE II—*continued*

Dose (μmoles/kg)	Control rate	Drug/Control	Method	Strain	References
26	0.03	1.1	Fl.cr.:tilt	DBA	Oliverio & Castellano (1974)
26.6	0.03	0.9	Fl.cr.:tilt	DBA	Castellano & Oliverio (1975)
Mean		1.0			
			30.1–100 μmoles/kg		
35	0.03	1.0	Fl.cr.:tilt	DBA	Castellano, Llovera, & Oliverio (1975)
52	0.03	0.8	Fl.cr.:tilt	DBA	Oliverio & Castellano (1974)
53	0.03	0.9	Fl.cr.:tilt	DBA	Castellano & Oliverio (1975)
70	0.03	1.1	Fl.cr.:tilt	DBA	Castellano, Llovera, & Oliverio (1975)
Mean		1.0			

[a]Run.wh. = the rotations of a running wheel as in Eidelberg, Ersparmer, Kreinick, & Harris (1975).

For column headings and other abbreviations, see Table I.

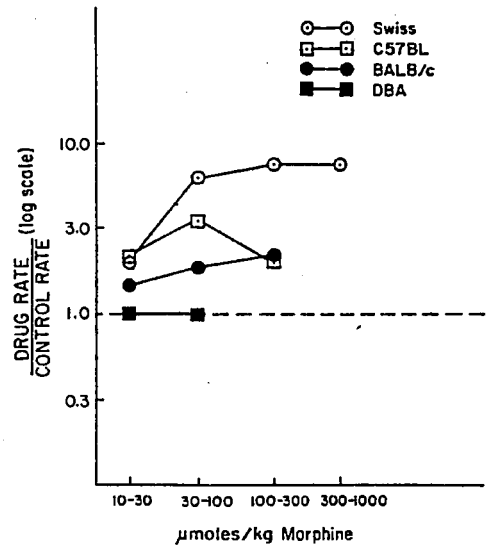

Fig. 5. The mean effect of morphine on SMA in four strains of mice (data from Table II). Abscissa: dose in μmoles/kg of body weight, pooled over one-half log unit ranges; ordinate: ratio of the rate of SMA following drug administration to the rate of SMA under control conditions; 2.6 μmoles/kg morphine base = 1 mg/kg morphine·SO_4.

Again, the question can be asked if these differences can be accounted for on behavioral terms; that is, is the difference attributable to the control level of activity? To answer this question, data from Table II were replotted as a function of the control rate of responding (Dews, 1964). The effects of a range of doses (30–100 μmoles/kg) were plotted to obtain enough points to make a meaningful comparison (Fig. 6). Unlike the results obtained with amphetamine, the points do not appear to be well mixed, and the points representing the Swiss and C57BL strain are practically all above the regression line ($y = -0.36x - 0.09$). The points for the DBA strain are all below the line, although they are all at the same control rate. Only the points representing the BALB/c strain appear to be somewhat scattered around the regression line. The failure to show that the different effects of morphine in the four strains could be accounted for by a single regression line relating drug effect to control rate or level of SMA (Fig. 6) emphasizes the significance of the findings for amphetamine.

It could be said that the failure to show a single rate-dependent function across strains following morphine administration may be due to the pooling of data using different methods and the wide dose range. Two studies reported morphine dose-response relationships in at least three strains, making a direct comparison

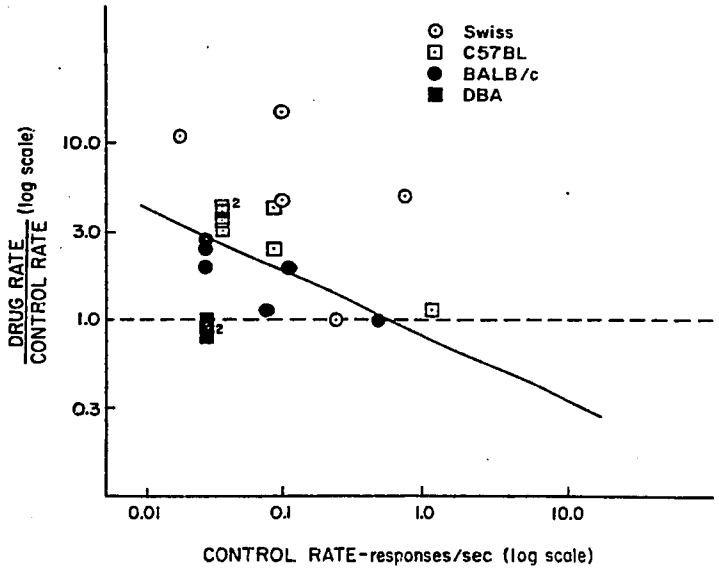

Fig. 6. The dependence of the effect of morphine on the control rate of SMA in four strains of mice over a dose range of 30–100 μmoles/kg (data from Table II). Data plotted as in Fig. 2. The regression line was calculated by the method of least squares: $y = -0.36x - 0.09$.

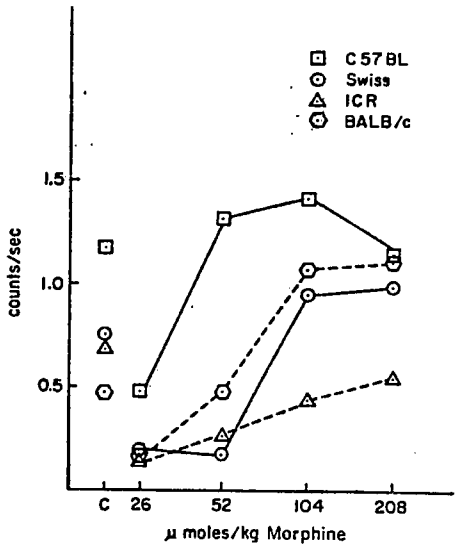

Fig. 7. The effect of morphine on SMA in four strains of mice. (Replotted from Eidelberg, Ersparmer, Kreinick, & Harris, 1975.) Abscissa: dose in μmoles/kg of body weight on a log scale; ordinate: level of SMA plotted as counts/sec generated by a mouse in a running wheel. Points at C represent control rates.

of the dependency of the response on the control level of activity possible within a single study (Castellano & Oliverio, 1975; Eidelberg, Erspamer, Kreinick, & Harris, 1975). Figure 7 shows the data replotted from the study by Eidelberg *et al.* (1975) reporting the effects of morphine on motor activity in four strains of mice. There is considerable difference in the control level of activity between the four strains. This study is the only one listed in Table II which showed a decrease in activity at a dose of 26 μmoles/kg with C57BL, Swiss, and BALB/c mice. This discrepancy suggests that the value for the control activity might be inaccurate. However, at a dose of 104 μmoles/kg, there is a good separation of the effects of morphine in the four different strains.

If the data are replotted as a function of the control value, as given, the effect of morphine at 52 and 104 μmoles/kg is not closely related to the control rate (Fig. 8); there is considerable scatter around the regression line (52 μmoles/kg: $y = +0.18x - 0.23$; 104 μmoles/kg: $y = -0.53x + 0.02$). There is a slightly better fit at the 208 μmoles/kg dose (208 μmoles/kg: $y = -0.87x - 0.02$) but, in general, the effect of morphine across strains in this study is not as dependent on the control level of SMA as is the effect of amphetamine seen in other studies.

In the study by Castellano and Oliverio (1975), the effect of three doses of

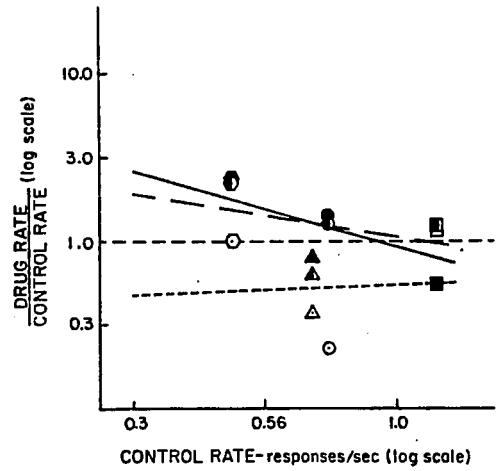

Fig. 8. The dependence of the effect of morphine on the control rate of SMA in four strains of mice. (Replotted from Eidelberg, Ersparmer, Kreinick, & Harris, 1975.) Data plotted as in Fig. 2. Regression lines were fitted by the method of least squares; 52 μmoles/kg: $y = +0.18x - 0.23$; 104 μmoles/kg: $y = -0.53x + 0.02$; 208 μmoles/kg: $y = -0.87x - 0.02$. Hexagon, BALB/c strain; triangle, ICR strain; circle, Swiss strain; rectangle, C57BL strain. Open symbols and dotted line represent the effect of 52 μmoles/kg; half-closed symbols and broken line represent the effect of 104 μmoles/kg; closed symbols and solid line represent the effect of 208 μmoles/kg.

morphine were determined in three different strains: C57BL, BALB/c, and DBA. The data from this study have been replotted and shown in Fig. 9. The control level of SMA was very low in all three strains which is probably due to the method used to determine the activity level. However, the level of activity in all three strains is quite similar. This cannot be said about the effect of morphine in the three strains. The differences in the effects of morphine at the 26 μmoles/kg and 53.2 μmoles/kg doses are quite large and cannot be accounted for on the basis of the control rate. The order of effect among the strains agrees quite well with the pooled data shown in Figs. 5 and 6. The increase in activity following a given dose of morphine in the 10–100 μmoles/kg range is greatest in C57BL, which is greater than BALB/c, which is greater than DBA. In addition, unlike the Eidelberg *et al.* (1975) study, low doses increase activity, in agreement with the pooled data shown in Figs. 5 and 6.

In conclusion, the effects of morphine in different strains of mice depend much less on the control level of SMA than amphetamine, and a much smaller part of the different effects observed in the different strains can be accounted for simply by differences in control behavior. Thus, strain differences in the physiological response to morphine may exist.

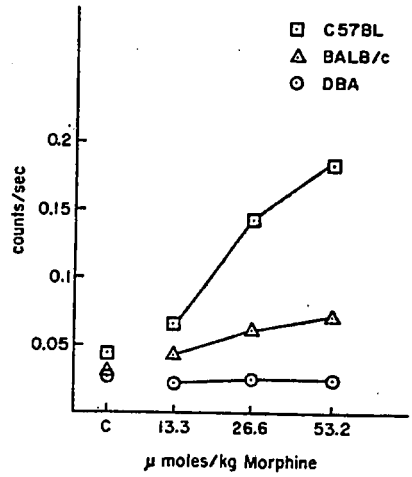

Fig. 9. The effect of morphine on SMA in three strains of mice. (Replotted from Castellano & Oliverio, 1975.) Abscissa: dose in μmoles/kg of body weight on a log scale; ordinate: level of SMA plotted as counts/sec generated by a mouse crossing from one side of the chamber to the other causing the chamber to tilt on an access and activate a microswitch.

IV. SCHEDULE-CONTROLLED BEHAVIOR IN THE MOUSE

The presentation of a reinforcing event upon a response increases the probability of that response occurring again. The relationship between the response and the reinforcing event is described as the schedule. The schedule can be programmed by the experimenter; so that the reinforcing event is presented following every *n*th response or upon a response occurring after an interval of time has elapsed or any combination of the two. The schedule comes to control both the rate and pattern of responding by the subject with different schedules producing different rates and patterns. Thus, the behavior has been called "schedule-controlled" behavior. (For a detailed account of the techniques used in the development of schedule-controlled behavior in laboratory animals, see Ferster & Skinner, 1957.)

Schedule-controlled behavior has proven to be useful in other species, but the techniques have not been applied to the mouse to the same degree as other species. Using schedule-controlled techniques, the behavior of a subject is controlled to the extent that the frequency of a specific response becomes quite predictable under steady-state conditions, and consistent patterns of responding emerge which are stable over many months. The administration of a drug to a

trained subject under these conditions can result in changes in both rate and/or pattern of responding compared with that seen in the absence of a drug. The effects of pharmacological agents on schedule-controlled behavior are readily reversible, and the rate and pattern of responding will return to the predrug state allowing repeated observations in the same subject. (For recent reviews on the use of schedule-controlled behavior techniques in the assessment of drug effects, see Dews & DeWeese, 1977; Iversen & Iversen, 1975; Thompson & Schuster, 1968.)

A. Responses Used

One of the earliest reported studies using schedule-controlled behavior in the mouse was the work of Anliker and Mayer (1956). The mice lived in the chamber 24 hr per day, and food pellets were delivered on a fixed-ratio (FR) 25 schedule of reinforcement of lever pressing. Examination of the cumulative record of pellet delivery showed regular patterns of feeding (groups of pellet deliveries separated by periods of few pellet deliveries) throughout the 24-hr day.

Since this initial report, there have been sporadic reports in the literature of mice responding under schedules of reinforcement involving three main types of responses: lever press, responses in which the mouse completes an electronic circuit (lick or touch), and interruption of a photocell beam. In the reports using lever press as a response (L. T. Anderson & Ressler, 1973; Anliker & Mayer, 1956; Butcher, Rhodes, & Yuwiler, 1972; Destrade, Soumireu-Mourat, & Cardo, 1973; Goodrick, 1967; Howard, 1973; Jaffard, Destrade, Soumireu-Mourat, & Cardo, 1974; Middaugh, Santos, & Zemp, 1975b; Randt & Quartermain, 1972; Schaefer, 1968; Singh, Lakey, & Sanders, 1974; Smart, 1970; Wenzel & Jeffrey, 1967), the force required to open or close the contacts ranges from 3 g (Schaefer, 1968) to 10 g (Howard, 1973) with a variety of values in between. It is difficult to evaluate the contribution of different force requirements on response rates of mice under different schedules, different reinforcing events, etc., and many reports do not provide the necessary information needed to make such comparisons. However, in those reports which provided the force required to operate the key and the response rates, the evidence would suggest that a force of 10 g is too much, and a force of 3–4 g is more suited to the mouse. Three reports (Howard, 1973; Middaugh *et al.*, 1975b; Smart, 1970) used a force requirement greater than 7 g. In these studies, response rates of less than 1 response per sec were reported for FR responding. In the only other reports which provided force requirements and response rates, Schaefer (1968) used a force of 3 g and Randt and Quartermain (1972) used a force of 4 g. In both of these reports, response rates of approximately 2 responses/sec were obtained under FR schedules. Response rates of 2 responses/sec are similar to that seen in other species under FR schedules. The force required of a 450-g pigeon to

operate a pigeon key is typically 15–20 g, and similar relative forces are used with rats and squirrel monkeys. In these three species, the force requirement is small relative to the capability of the subject. A force of 3 g for a 25-g mouse more closely resembles, although is still greater, the relative force requirements used with other species, but the mechanical nature of a lever makes a force of less than 3 g impractical.

Not surprisingly, a number of workers have sought responses which have essentially no force requirements. One such response involves the completion of an electronic circuit by the mouse. The use of minute amounts of current, barely noticeable to the mouse, does not in any way tend to suppress responding. One such response requires the mouse to bridge between two conductive elements by having the mouse touch a contact plate or a lever (Freund & Walker, 1972; Middaugh, Santos, Carrol, & Zemp, 1975a; Revusky, 1966). A modification of this technique requires the mouse to lick a drinking tube with each lick recorded as a separate response (Ray, 1970; Sidman, Ray, Sidman, & Klinger, 1966; Sprott, 1972). Another response requiring essentially no force is the interruption of a beam of light striking a photocell (Botticelli, 1977; Wenger, in press; Wenger & Dews, 1976). In general, higher response rates have been obtained using responses requiring no force. The measurement of published cumulative records by Sidman *et al.* (1966) and Ray (1970) of mice licking a drinking tube under a variable ratio (VR) schedule indicates that average rates of better than 3 responses/sec were obtained. Similarly, Sprott (1972) reported response rates of 2.4 responses/sec using licking as a response under a variable interval (VI) schedule. Wenger and Dews (1976) report response rates of 1.6 and 0.7 responses/sec for the FR and fixed-interval (FI) components, respectively, of a multiple schedule using the interruption of a photocell beam as a response.

There is some evidence that licking may be different than other responses commonly used. Licking may have an inherent biological frequency, which is relatively resistant to drug effects. Knowler and Ukena (1973) studied the effects of amphetamine in rats using licking as a response. Although high response rates were obtained, greater than 3 responses/sec, they were unable to show a decrease in rate with amphetamine. Thus, caution must be used when comparing drug effects on licking in the mouse to drug effects in other species using other responses.

B. Events Used to Maintain Responding

A variety of different events have been used to maintain responding in mice. The two most common events have been the presentation of food pellets and some form of milk. Noyes pellets (20 mg/pellet) have been used most commonly (L. T. Anderson & Ressler, 1973; Butcher *et al.*, 1972; Freund & Walker, 1972; Howard, 1973; Middaugh *et al.*, 1975a, 1975b; Singh *et al.*, 1974), but a 48-mg

pellet made of mostly dextrose was used by Smart (1970), and a 6-mg pellet was used by Destrade *et al.* (1973). In those reports using some form of milk, sweetened condensed milk has been the most commonly used, either undiluted (Sprott, 1972; Wenzel & Jeffrey, 1967) or diluted with water (Ray, 1970; Sidman *et al.*, 1966; Sprott. Clark, & Wimer, 1970). Wenger and Dews (1976) and Bottecelli (1977) used undiluted evaporated milk. It is not possible to assess the desirability of one type of food over another at this time.

In the reports where food pellets or milk were used to maintain the behavior, mice were generally food deprived until a body weight equivalent to 80% of their free feeding weight was achieved. The ease of the initial training varies considerably with the degree of deprivation; however, once stable performance has been achieved, the degree of deprivation does not appear to be as important. For training, a body weight equivalent to about 75% of free feeding weight is about optimum. If the weight is reduced much below this level, the activity of the mouse is reduced. Using C57BL type mouse, this degree of deprivation is achieved with about 65 hr of total food deprivation. If all the food is taken away from a mouse on a Friday afternoon, the desired weight loss is achieved by Monday morning. This degree of deprivation can be maintained by supplementing the caloric intake of the mouse at the end of the experimental day. The supplemental food required can be given to individual mice even when they are housed 4–5 mice/cage, providing they are all approximately the same body weight. Mice can be treated as a group under these conditions, and when the supplemental food is given in the form of 500-mg pellets, no one mouse in the cage has ever been observed to gain weight at the expense of another animal in the cage. With C57BL type mice, weighing 25–30 g, when given free access to food, a body weight equivalent to 75 or 80% of their free feeding weight is maintained by giving three to four 500-mg food pellets/mouse in the cage (G. R. Wenger, unpublished observation). This greatly reduces the amount of time and labor required, as well as cage space required to carry out a continuing experiment. This is an important advantage when a large group of animals is being used.

When the desired degree of deprivation has been maintained, response rates reported in the literature vary from 0.07 responses/sec reported by Freund and Walker (1972) for mice responding under a tandem FI 1.5-sec FR 1 schedule of food pellet presentation to a response rate of greater than 3 responses/sec reported by Sidman *et al.* (1966) and Ray (1970) for mice responding under a VR 194 schedule of milk presentation.

Other events have been used to maintain behavior of mice. Randt and Quartermain (1972) used water presentation under FR schedules to maintain the behavior of mice which were 72 hr water deprived. FR values of 1–32 were used with response rates of 0.4 responses/sec under the FR 1 schedule to approximately 1.7 responses/sec under the FR 32 schedule. In the same study, electrical

stimulation of the brain, 60 Hz, 0.3 sec duration, 30–150 μA was used to maintain behavior. Under a FR 1 schedule of brain stimulation, response rates varied from 0.2 to 0.5 responses/sec. At higher FR values, inspection of the cumulative record indicates that the response rates obtained were not as high as those obtained when H_2O was used as a reinforcer at equivalent FR values.

Revusky (1966) used the presentation of heat to mice in a cold room to maintain responding under an FR 1 schedule; no response rate was reported. Goodrick (1967) used the presentation of light to maintain the responding of mice housed in the dark on an FR 1 schedule; no response rate was reported.

The behavior of mice can be suppressed by the presentation of a stimulus associated with a brief electrical shock (L. T. Anderson & Ressler, 1973; Ray,

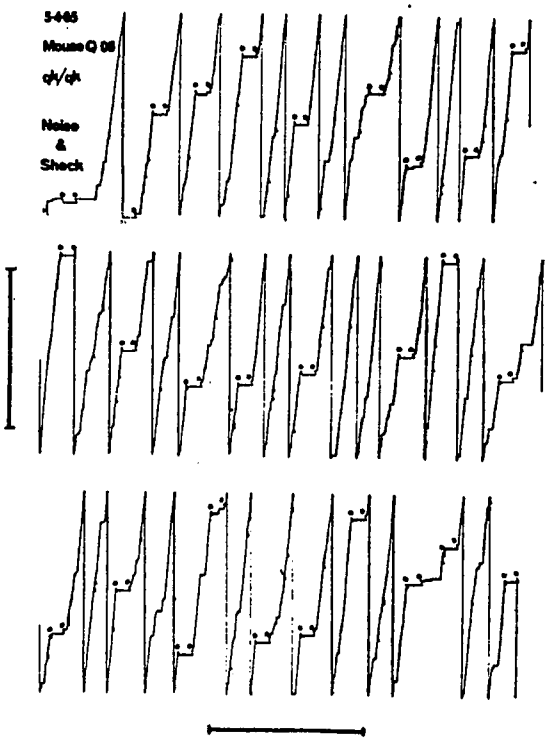

Fig. 10. Cumulative record of the quaking mouse's licking behavior under the VR 194 schedule of reinforcement. The pairs of dots indicate the beginning and end of each warning signal. Vertical line: 369 responses; horizontal line: 10 min. (From Sidman, Ray, Sidman, & Klinger, 1966, with permission.)

1970; Sidman *et al.*, 1966; Sprott *et al.*, 1970). In the studies by Sidman *et al.* (1966) and Ray (1970), a modification of a procedure originally described by Estes and Skinner (1941) was used to determine visual and auditory thresholds of neurologic mutant mice. Mice were trained to respond under a VR schedule of milk presentation. Response rates of greater than 3 responses/sec were maintained under this schedule. At predetermined times during the experimental session, a 1-min stimulus was presented followed by an unavoidable electric shock presented through a grid floor. As seen in Fig. 10, responding was almost totally suppressed for the duration of the stimulus presentation.

C. Schedules of Reinforcement

As mentioned above, a variety of schedules have been used to maintain responding of mice. FR and VR schedules have been used (Anliker & Mayer, 1956; Butcher *et al.*, 1972; Destrade *et al.*, 1973; Goodrick, 1967; Howard, 1973; Jaffard *et al.*, 1974; Middaugh *et al.*, 1975a, 1975b; Randt & Quartermain, 1972; Ray, 1970; Revusky, 1966; Schaefer, 1968; Sidman *et al.*, 1966; Singh *et al.*, 1974; Smart, 1970; Sprott, 1972). Ratio values have ranged from FR 1 to VR 194 (range = 8-525). The reported patterns of responding have been similar to those reported for other species (see Fig. 10), and the response rates have ranged from 0.02 responses/ sec under an FR 1 schedule (Destrade *et al.*, 1973; Singh *et al.*, 1974) to 2.0 responses/sec under an FR 30 schedule (Butcher *et al.*, 1972) to better than 3 responses/sec under a VR 194 schedule (Sidman *et al.*, 1966).

VI schedules have also been used to maintain responding (L. T. Anderson & Ressler, 1973; Freund & Walker, 1972; Sprott, 1972; Sprott *et al.*, 1970; Wenzel & Jeffrey, 1967), with interval values ranging from 10 to 60 sec. The reported patterns of responding are similar to those observed in other species: a relatively continuous rate of responding with few pauses. Response rates have ranged from 0.37 responses/ sec for mice responding under a VI 10-sec schedule to 2.4 responses/sec for mice responding under a VI 30-sec schedule.

There are two reports which used differential reinforcement of low rate (DRL) schedules (Freund & Walker, 1972; Howard, 1973). Both reports used a DRL value of 20 sec, and both studies reported that 20-30% of all responses were longer than the DRL requirement and, therefore, reinforced.

Several reports have used more complex schedules. Smart (1970) reported using a delay-of-reinforcement procedure. In this report, the mouse responded under a FR 5 schedule. Upon the completion of the fifth response, a visual cue was turned on, signaling the start of the delay of reinforcement period which ranged in value from 5 to 26 sec. The necessary information to compute response rates and to determine patterns of responding was not provided in the published

report. Freund and Walker (1972) reported having mice respond under a tandem FI 1.5-sec FR 1 schedule. The average response rate under this schedule was 0.07 responses/sec.

There are several reports of multiple schedules with mice. Jaffard *et al.* (1974) reported using a mult FR 1 S^{Δ} schedule. In this schedule S^{D} periods in which the schedule of reinforcement was FR 1 alternated with equal periods of S^{Δ}. Mice were able to achieve a 78% level of discrimination; 78% of all responses were made during the S^{D} periods. Wenger and Dews (1976), Wenger (in press), and Botticelli (1977) reported using mult FR-FI schedules with mice. In all three reports, response rates were approximately 0.6–0.7 responses/sec during the FI 300- or 600-sec component and approximately 2 responses/sec during the FR 30 component. Patterns of responding were similar to those reported in other species. A cumulative record of responding of a mouse under a mult FR 30–FI 600-sec schedule is shown in Fig. 11. Average response rates during this session were 4.4 and 0.6 responses/sec for the FR 30- and FI 600-sec components, respectively.

There also is one report in the literature reporting adjunctive drinking in mice (Palfai, Kutscher, & Symons, 1971). In this study, a food pellet was delivered to a mouse every 150 sec independent of any response (FT 150 sec). During the 3-hr session, the water intake of the mice ranged from 40 to 101% of their body weight.

Thus, there is much to be done using schedule-controlled behavior in the mouse. The techniques used in other species appear to be readily adaptable with minor modifications due to the relative size of the mouse. The use of schedule-controlled behavior in the mouse would provide more precise control over the

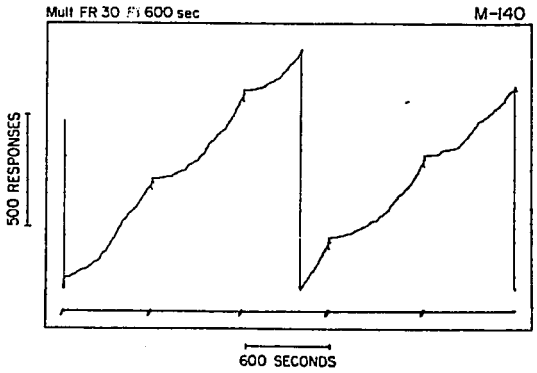

Fig. 11. Cumulative record of responding of mouse M-140 under a mult FR 30–FI 600-sec schedule.

rate of responding compared with SMA, allowing an experimenter to compare the behavioral effects of drugs in different genetic strains without the degree of variation in response rates seen in SMA.

The successful demonstration of schedule-controlled behavior in the mouse provides a good alternative for those investigators interested in behavioral toxicology. As discussed earlier, the mouse has many advantages as a laboratory animal in the field of toxicology. The use of schedule-controlled behavior in the mouse will allow a more detailed analysis of the behavioral effects of toxic agents than is possible with more routinely studied behaviors, such as SMA or CAR.

At the present time, however, more studies on the behavioral effects of therapeutic drugs on schedule-controlled behavior in the mouse must be done. It must be determined if any major differences in the behavioral effects of drugs exist between mice and other more commonly studied species, such as rats, pigeons, and monkeys. Without this information, the behavioral effects of new drugs or toxic agents cannot be interpreted in the context of the rest of behavioral pharmacology.

V. DRUG EFFECTS ON SCHEDULE-CONTROLLED BEHAVIOR IN THE MOUSE

One of the earliest reports on drug effects on schedule-controlled behavior in the mouse reported the effects of reserpine on responding maintained by a FR 30 schedule (Butcher *et al.*, 1972). Mice were trained to respond under a FR 30 schedule of food pellet presentation. Twenty-four hours before the session, mice were given 4.1 μmoles/kg (2.5 mg/kg) reserpine. Responding was totally suppressed 24 hr after administration and gradually returned to 40% of the control value over the next 7 days. Since this was the only dose given, the effects of lower doses in the same animals are not known, and it is impossible to interpret the results in the mouse compared to other species. However, it can be said that the dose is probably much higher than necessary to suppress responding under an FR 30 schedule. Dews (1956) reported suppressed responding in pigeons under a mult FR FI schedule, 30 hr after the administration of 0.3 μmoles/kg reserpine. Similarly, Sidman (1956) reported suppressed responding of rats responding under a FR 10 schedule 24 hr after 0.15 μmoles/kg reserpine. However, Butcher *et al.* (1972) were able to partially reverse the reserpine-induced suppression by the administration of high doses of DOPA plus a peripheral decarboxylase inhibitor. High doses of 5-hydroxytryptophan plus a peripheral decarboxylase inhibitor had no effect on the reserpine-induced suppression of responding.

More recently, Wenger and Dews (1976) determined the effects of *d*-amphetamine, pentobarbital, phencyclidine, and ketamine in mice responding

under a mult FR 30- FI 300-sec schedule. The effects of amphetamine on responding of mice under this schedule are similar to those reported in other species (Fig. 12). Amphetamine increased responding in the FI component at low doses and decreased responding at high doses. Responding under the FR schedule was decreased at doses lower than those required to decrease FI responding. The effects on responding under the FI schedule were dependent on the rate of responding (Fig. 13). Low rates of responding were increased and high rates of responding were decreased. Thus, as in other species, the effects of amphetamine are dependent on the rate of behavior that exists under control conditions. These results are in agreement with those reported for amphetamine in pigeons (McMillan, 1968, 1969; Rutledge & Kelleher, 1965; Smith, 1964), rats (Clark & Steele, 1966), and monkeys (Cook & Kelleher, 1962; Kelleher & Morse, 1964).

Pentobarbital increased the rate of responding (12 μmoles/kg, 3 mg/kg as the Na salt) under both the FR 30- and FI 300-sec component in the mouse. As the dose was increased, the response rates were decreased in both components. These results differ from those reported for pigeons (Leander & McMillan, 1974; McKearney, 1972; Morse, 1962; Rutledge & Kelleher, 1965) and monkeys (Verhave, 1959) responding under a mult FR FI schedule, in that the greater

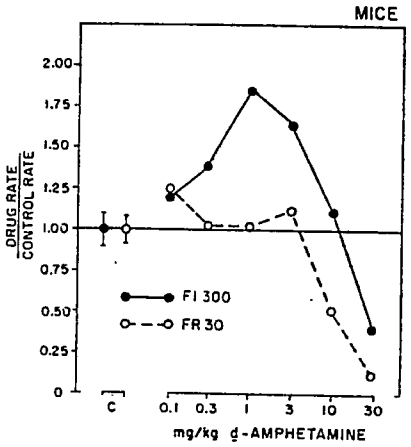

Fig. 12. Effect of *d*-amphetamine on the average rate of responding in each component of the mult FR 30–FI 300-sec schedule. Abscissa: dose in mg/kg of body weight on a log scale; ordinate: ratio of the average rate of responding following drug administration to the rate of responding on nondrug control days. Vertical lines at C represent the mean ±2 S.E.M. The solid horizontal line represents the mean control value. Each point represents the mean of single determinations in each of 2 mice. Mean control rates of responding were 0.62 responses/sec and 1.40 responses/sec for the FI and FR, respectively. (From Wenger & Dews, 1976, with permission.)

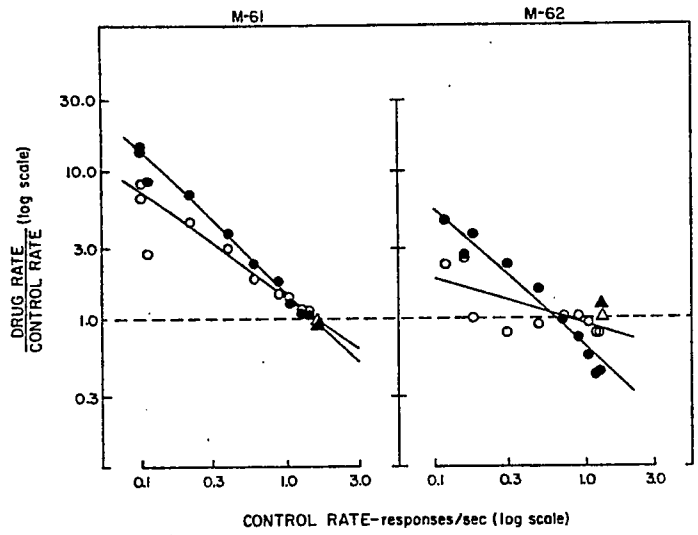

Fig. 13. The dependence of the effect of *d*-amphetamine on the control rate of responding in mice M-61 and M-62. Abscissa: average rate of responding on a log scale in successive 30-sec periods of the FI 300-sec schedule (circles), and under the FR 30 response schedule (triangles); ordinate: ratio of the average rate after drug administration to the average rate on nondrug control days. Open symbols (circles and triangles) represent the effect of 1.6 μmoles/kg; closed symbols (circles and triangles) represent the effect of 16 μmoles/kg. Regression lines were fit by the method of least squares using the points from the FI schedule.

sensitivity of FI responding, compared to FR responding, to the rate decreasing effects of pentobarbital was not observed.

Phencyclidine (1.25–42 μmoles/kg, 0.3–10 mg/kg as the HCl salt) and ketamine (110–370 μmoles/kg, 30–100 mg/kg as the HCl salt) increased FI responding, and higher doses decreased FI responding. FR responding was unaffected at doses less than or equal to 4.2 μmoles/kg phencyclidine and 37 μmoles/kg ketamine. Higher doses of phencyclidine and ketamine decreased FR responding. Thus, the doses which decreased FR responding were lower than those which decreased FI responding. The effects of phencyclidine and ketamine in the mouse were dependent upon the control rate of responding. These results are in agreement with those reported in the pigeon responding under a similar schedule (Wenger, 1976).

In a preliminary report by Botticelli (1977), the effects of morphine and naloxone were reported on the responding of mice under a mult FR 30- FI 600-sec schedule of food presentation. Morphine produced dose-dependent decreases in FR responding over a dose range of 0.8–78 μmoles/kg (0.3–30 mg/kg

as morphine·SO_4). Low doses of morphine (0.8–7.8 μmoles/kg) increased response rates during the FI component, while doses of 26 and 78 μmoles/kg decreased FI responding. Thus, the effects of morphine in the mouse appear to be consistent with the reported effects of morphine in other species responding under similar schedules (S. R. Goldberg, Morse, & Goldberg, 1976; Holtzman & Villarreal, 1973; McMillan & Morse, 1967; Tsou, 1963; Woods, 1969). Naloxone was studied over a dose range of 0.8–280 μmoles/kg (0.3–100 mg/kg naloxone·HCl). A small decrease in FR and FI responding was observed over a 100-fold range; the decreases were not dose-related.

Wenger (in press) examining the effects of atropine (0.9–518 μmoles/kg, 0.3–180 mg/kg atropine · SO_4) and scopolamine (0.08–1456 μmoles/kg, 0.03–560 mg/kg scopolamine·HBr) on responding of mice under a mult FR 30- FI 600-sec schedule, reported that both atropine and scopolamine produced increases in FI responding at low doses and decreases in FI responding at very high doses. Atropine, but not scopolamine, decreased FR responding at low doses in a dose-dependent manner. The effect of both atropine and scopolamine on FI responding were dependent on the control rate of responding. Low response rates in the early portions of the FI were increased to a greater extent than the high response rates in the terminal portions of the FI. Effects on responding were observed at low doses of atropine (2.9 μ moles/kg) and scopolamine (0.3 μmoles/kg). The maximum increases in FI responding were observed after 86 μmoles/kg atropine and after 2.6 μ moles/kg scopolamine, while the doses required to decrease FI responding below the control rate were >518 μmoles/kg and >1456 μmoles/kg for atropine and scopolamine, respectively. The effects of atropine and scopolamine on FI responding in the mouse are similar to the effects reported for FI responding in the pigeon (Vaillant, 1967) and the rat (Boren, 1961; Boren & Navarro, 1959). Similarly, the effects of atropine on FR responding in the mouse are consistent with reports in other species (Boren & Navarro, 1959; Pradhan & Roth, 1968; Vaillant, 1967).

Thus, the few published reports on drug effects on schedule-controlled behavior in the mouse would indicate that there are no major species differences between the mouse and other more extensively studied species. Compared to SMA as commonly measured, some schedule-controlled behavior would appear to be more sensitive to drug effects in the mouse. Amphetamine (Fig. 1 and Table I) does not produce an effect on SMA in the C57BL strain at doses below 10 μmoles/kg, while Wenger and Dews (1976) reported effects on responding of C57BL mice under the FI component of a mult FR FI schedule at doses of 0.3 mg/kg or 1.6 μmoles/kg (Fig. 12). In the same study, nearly a 2-fold increase in FI responding was observed at 1 mg/kg or 5.4 μmoles/ kg. Morphine increases SMA in the C57BL strain over a dose range of approximately 10–100 μmoles/kg with a peak effect observed at approximately 50–60 μmoles/ kg (Fig. 5 and Table

II). Botticelli (1977) reported effects on responding of C57BL mice under both components of a mult FR FI schedule at doses as low as 0.8 μmoles/ kg, and the maximum increase in FI responding was observed at less than 20 μmoles/ kg. Atropine is reported to be without effect on SMA at doses below 40 μmoles/ kg in NMRI mice (Waldeck, 1974), and Ahtee and Shillito (1970) report no effect on SMA in albino mice at doses up to 58 μmoles/kg. Wenger (in press), on the other hand, reported effects of atropine on responding under both components of a mult FR FI schedule in C57BL mice at doses of 3 μmoles/kg. Thus, it would appear as if the potential for the use of schedule-controlled behavior in the mouse is good because of the practicality of using the mouse in such areas as behavioral toxicology and because of the apparent sensitivity to drug effects as compared with SMA, as commonly measured.

VI. SUMMARY

The effects of drugs on SMA have been generally consistent, but there are examples of differences in the responses observed in different strains following the administration of several drugs. The reason for these reported strain differences can be of at least two major types: differences which can be attributed to differences in the control behavior, as seen with amphetamine, and differences which cannot be accounted for by known differences in the behavior, as seen with morphine. Thus, it is imperative that behavioral variables be controlled in any study involving drug effects in different strains.

Although there has been very little work on the effects of drugs on schedule-controlled behavior in the mouse, the existing literature strongly suggests that techniques for studying schedule-controlled behavior are readily adapted to the mouse. The effects of drugs on schedule-controlled behavior in the mouse have in general been in good agreement with the results obtained in other species, and effects have been observed on some schedule-controlled behavior at doses lower than those required to affect SMA, as commonly measured.

It is likely that the mouse will become an increasingly important species in behavioral pharmacology and toxicology. The mouse offers many practical advantages, in addition to the availability of pure genetic strains which should reduce subject-to-subject variation in drug effects to a considerable degree. In addition, the possibility that different strains may exhibit different sensitivities to different drugs, as shown for morphine, may be a useful adjunct in behavioral pharmacology and toxicology and may prove to be a useful approach in determining the neuronal substrate of drug action. The use of schedule-controlled techniques to control behavioral variables in different strains of mice will be of utmost importance in this endeavor.

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