BEHAVIORAL BIOLOGY 17, 463-471 (1976), Abstract No. 5300

# Comparison of the Effects of *d*-Amphetamine and Lysergic Acid Diethylamide in Two Strains of Rats Having Different Behavioral Baselines[1]

H. A. TILSON[2], A. S. MAISEL, M. G. JOURDAN, and R. H. RECH

*Department of Pharmacology, Michigan State University, East Lansing, Michigan 48823*

Fisher (*F*) and Sprague Dawley (*SD*) rats were trained to press a lever on a fixed interval (FI) schedule of food reinforcement or to postpone electric footshock on an unsignaled, continuous avoidance schedule. *F* strain rats responded on the FI schedule at a lower rate than the *SD* rats. Responding of *F* rats was increased by low doses (0.075-0.10 mg/kg, ip) of *d*-amphetamine that had no effect on *SD* rats. However, linear regression analysis of successive quartiles of FI responding indicated little difference between strains in terms of the rate-dependent effects of *d*-amphetamine (0.075-1.0 mg/kg, ip). In the continuous avoidance procedure, *F* strain rats had a baseline response rate that was almost twice that of *SD* rats. However, *F* strain rats were more sensitive than *SD* rats to the rate-increasing effects of *d*-amphetamine (0.1-1.0 mg/kg). Under both schedules of operant responding, *SD* rats appeared to be more sensitive than *F* rats to the effects of LSD (0.01-0.8 mg/kg, ip). Strain-related differences in sensitivity to the behavioral effects of *d*-amphetamine and LSD were not predicted from the observed differences in control baseline.

Amphetamine has been reported to have a differential effect on operant behavior depending upon baseline response rates. For example, Kelleher and Morse (1968) have shown that low frequency operant behavior is increased by doses of amphetamine which have little effect on, or even decrease high baseline response rates. This phenomenon of rate-dependency has been demonstrated in numerous species for several types of schedule-controlled behaviors maintained by various reinforcers (Kelleher and Morse, 1968; Heffner *et al.*, 1974). In spite of the general relationship between rate of response and drug effect, there are numerous reports that are inconsistent with a simple rate-dependency hypothesis. For example, behavior under the

[1]Supported in part by Grants NS-10323 from NINDS and MH-22093 from NIMH.

[2]Author to whom reprint requests should be sent. Present address: Pharmacology Research, Bristol Laboratories, Syracuse, New York 13201.

control of external stimuli appears to be affected less by amphetamine than behavior presumed to be controlled by internal cues (Laties and Weiss, 1966; Carey and Kritkausky, 1972; Thompson and Corr, 1974). A low rate of responding suppressed by punishment is reportedly unaffected or further suppressed following amphetamine (Geller and Seifter, 1960; Hanson *et al.*, 1967), although rate-dependent effects on punished behavior have been observed under some circumstances (McMillan, 1973). Finally, Evans *et al.* (1973) reported recently that the rate-dependent effects of methamphetamine varied according to the light or dark periods of the rats' diurnal cycle.

The rate-dependency hypothesis has been widely invoked as an explanation for individual variability in response to amphetamine, as well as a possible explanation for the seeming "paradoxical" effect of stimulants in hyperkinetic children (Glick and Milloy, 1973). However, few investigators have attempted to study possible neurobehavioral differences in individuals having high or low baseline response rates. The purpose of this study was to compare the rate-dependent effects of *d*-amphetamine and those of *d*-lysergic acid diethylamide-25 (LSD) in two different strains of rats. Animals from the Fisher and Sprague-Dawley strains were chosen since previous reports have demonstrated that they differ in regard to several neurochemical, psychopharmacological, and behavioral parameters (Rosecrans and Schechter, 1972; Segal *et al.*, 1972, 1975; Barrett *et al.*, 1973; Tilson and Rech, 1974).

## METHODS

*Subjects.* Seven male, albino Sprague-Dawley (*SD*) and seven male Fisher (*F*) strain rats obtained from Spartan Farms (Haslett, Michigan) and Microbiological Associates (Walkerville, Maryland), respectively, were used as subjects. The animals weighed 250-300 g at the beginning of the experiment and were housed in pairs in air-conditioned quarters under a 12 hr light-dark cycle (light 8 AM to 8 PM). Water was freely available to all animals in the home cages. Laboratory rat chow was also freely available to animals that were trained to respond on a negatively reinforced schedule, while rats trained on a positively reinforced schedule were maintained at a reduced body weight with supplementary feedings following behavioral sessions.

*Apparatus and drug injections.* One-hour behavioral sessions were conducted in two-lever operant chambers described previously (Tilson and Rech, 1973; Marquis *et al.*, 1973). *d*-Amphetamine sulfate (K and K Labs, Plainview, New York) or *d*-LSD tartrate (supplied through the auspices of FDA/PHS Psychotomimetics Agent Advisory Committee) was dissolved in isotonic saline (NaCl) and injected ip in a volume of 1 ml/kg immediately before placing the subject into the operant chamber. The dose-related effects of *d*-amphetamine and LSD on continuous avoidance and fixed-interval responding were

determined, with *d*-amphetamine being investigated prior to LSD. The rats received each dose of the two drugs at least twice in a random order. At least 2 days separated drug injections during which NaCl was administered.

*Fixed-interval (FI) responding.* Three *F* and three *SD* rats were food-deprived to 75-80% of their free feeding body weight and trained to press a lever for 45 mg food pellets on a FI 60 sec schedule of reinforcement. Each session was terminated after 50 reinforcers so that all subjects received an equal number of reinforcers during training and subsequent control sessions. Responding during consecutive 15 sec segments of each 60 sec interval was measured by means of a printout counter. Regression line analysis of drug-induced changes in response rate was determined by a computer-assisted program which plotted on a log-log scale the two group's average drug rates in the four successive 15 sec segments (for 50 reinforcers) as percentages of the NaCl control rates obtained on preceding days.

*Unsignaled Continuous Avoidance.* Four *SD* and four *F* rats were trained to press a lever to postpone electric footshock (2.0 mA) applied to the grids of the operant chamber (Tilson and Rech, 1973). The response to shock (R-S) interval was 30 sec, the shock to shock (S-S) interval was 5 sec, and the shock duration was 0.2 sec. The total number of responses emitted and the shocks delivered during hourly sessions were compiled on digital counters.

## RESULTS

*Control response rates.* Under NaCl control conditions there were obvious differences in the overall response rates of the two strains of rats. For example, the average rate of continuous avoidance responding for the *F*-strain rats was 7.1 ± 0.5 responses/min (mean ± SE), which is statistically greater than the 4.4 ± 0.9 responses/min rate of the *SD* rats. In contrast, the overall response rate for the *F* rats responding on the food-reinforced FI 60 sec schedule was 5.8 ± 0.4 responses/min, as compared to the 8.9 ± 0.8 responses/min emitted by the *SD* rats. The difference between the control rates of FI responding was also statistically significant (*t* test, $P < 0.05$). Segmental analysis of 50 consecutive 60 sec intervals indicated that responding in each 15 sec quartile by *F* strain rats was statistically lower than that of the *SD* rats (Table 1). The most prominent difference in responding appeared to be in the first 30 sec of the interval, during which the *F* strain rats responded at less than one response/min.

*Drug effects on FI responding.* Although the change was not statistically significant, 0.075 mg/kg of *d*-amphetamine increased the average rate of FI responding by *F* rats (118% of control; Table 2). Larger doses of *d*-amphetamine (0.10 and 0.30 mg/kg) produced significant increases in responding, while 0.50 and 1.0 mg/kg decreased the overall response rate. The *SD* rats also

TABLE 1

Average NaCl Control Response Rates during Successive 15 Second Segments of a Fixed-Interval 60 Second Schedule of Reinforcement

| | Mean response rate (responses/min) ± SE[a] (successive 15 second segment) | | | |
|---|---|---|---|---|
| Strain of rat | 1 | 2 | 3 | 4 |
| Sprague-Dawley | 1.7 ± 0.5 | 2.0 ± 0.2 | 6.3 ± 1.0 | 25.6 ± 2.7 |
| Fisher | 0.4 ± 0.1[b] | 0.9 ± 0.3[b] | 3.7 ± 0.4[b] | 18.2 ± 1.2[b] |

[a]An average NaCl control rate was determined for each subject during dose-response evaluation of LSD and *d*-amphetamine. Group means ± SE are derived from two values per each of three subjects.

[b]Statistically different than corresponding mean of Sprague-Dawley rats (*t* test, $P < 0.05$).

showed an inverted-U-shaped dose response curve similar to the *F* rats, but the curve was displaced to the right. That is, the response rates of the *SD* rats were not markedly affected at 0.075 and 0.100 mg/kg of *d*-amphetamine while the largest increase in rate occurred at 0.300 mg/kg. Lesser increments or decreases in the overall rate followed 0.500 and 1.000 mg/kg. *d*-Amphetamine produced a rate-dependent effect on the FI responding of both strains of rats. That is, when overall response rates were increased, lower response rates were increased more than higher rates. Thus, the corresponding regression line resulting from an analysis of control rate and percentage change from control had a negative slope.

The effects of LSD on FI 60 sec responding by *SD* and *F* rats are also seen in Table 2. LSD significantly altered the overall rate of *F* rats at the 0.02 mg/kg dose only, while having no statistically reliable effect at the other doses tested. The overall response rate of *SD* rats was increased significantly at 0.02 and 0.05 mg/kg of LSD while 0.10 mg/kg tended to decrease responding by most *SD* rats. Analysis of responding during consecutive 15 sec segments indicated a slight rate-dependent effect by LSD in both strains at 0.02 and 0.05 mg/kg. However, the maximal changes in slope were less than half those observed following administration of *d*-amphetamine.

*Drug effect on continuous avoidance responding.* In spite of the higher control baseline rate of responding, the *F* strain of rats (7.1 responses/min) were more sensitive to the rate-increasing effects of *d*-amphetamine than the *SD* rats (control rate of 4.4 responses/min). As seen in Table 3, *d*-amphetamine (0.1-1.0 mg/kg) produced significant, dose-related increases in response rate of *F* strain rats. On the other hand, significant increases in responding by *SD* rats were noted at 0.25 and 0.50 mg/kg of *d*-amphetamine only, while the

TABLE 2

The Effects of *d*-Amphetamine and LSD on the Fixed Interval Responding of Fisher and Sprague-Dawley Rats

| | Fisher rats | | | | Sprague-Dawley rats | | | |
|---|---|---|---|---|---|---|---|---|
| Drug and dosage (mg/kg) | NaCl control rate ± SE | Rate after drug ± SE | (%) Control | Slope (degrees)[a] | NaCl control rate ± SE | Rate after drug ± SE | (%) Control | Slope (degrees)[a] |
| *d*-Amphetamine | | | | | | | | |
| 0.075 | 7.3 ± 0.8 | 8.6 ± 0.7 | 118 | −10.0 | 10.2 ± 0.7 | 10.5 ± 0.2 | 103 | −5.2 |
| 0.100 | 6.1 ± 0.5 | 7.3 ± 0.3[c] | 120 | −4.1 | 8.0 ± 0.3 | 8.1 ± 0.2 | 101 | +0.9 |
| 0.300 | 7.8 ± 0.2 | 10.1 ± 0.6[c] | 129 | −10.9 | 9.4 ± 0.8 | 12.5 ± 0.2[c] | 133 | −25.2[b] |
| 0.500 | 5.7 ± 0.2 | 3.1 ± 0.3[c] | 54 | −17.6 | 10.3 ± 1.4 | 13.2 ± 0.8 | 128 | −14.5 |
| 1.000 | 5.2 ± 0.4 | 3.0 ± 0.2[c] | 58 | −4.7 | 9.1 ± 0.9 | 7.1 ± 0.8[c] | 78 | −11.8 |
| LSD | | | | | | | | |
| 0.01 | 4.3 ± 0.5 | 4.9 ± 0.3 | 114 | +6.8 | 7.1 ± 0.7 | 8.3 ± 0.2 | 117 | +0.4 |
| 0.02 | 4.6 ± 0.6 | 6.8 ± 0.2[c] | 148 | −2.4 | 8.3 ± 0.9 | 11.0 ± 1.2[c] | 133 | −2.0 |
| 0.05 | 5.6 ± 0.4 | 5.4 ± 0.6 | 96 | −8.4 | 8.5 ± 0.8 | 14.9 ± 1.8[c] | 175 | −10.6 |
| 0.10 | 6.3 ± 0.1 | 6.2 ± 0.5 | 98 | −1.0 | 9.8 ± 0.8 | 8.7 ± 0.5 | 89 | −1.6 |

[a]A regression line was determined by plotting on a log-log scale each subject's drug-induced response rate as a percentage of the preceding day's NaCl control rate (Y) as a function of the absolute NaCl control rate (X). Slope of the regression line was determined by the method of least squares.

[b]The slope of the regression line for the Sprague-Dawley rats is statistically different than the corresponding slope of the Fisher rats (*F*-test, $P < 0.05$).

[c]Statistically different from NaCl control (matched pair *t* test, $P < 0.05$).

[d]Statistically different from the corresponding mean of the Fisher rats (*t* test, $P < 0.05$).

TABLE 3

The Effects of *d*-Amphetamine and LSD on Continuous Avoidance Responding of Fisher and Sprague-Dawley Rats

| Drug and dosage (mg/kg) | Fisher rats | | | Sprague-Dawley rats | | |
|---|---|---|---|---|---|---|
| | NaCl control rate ± SE | Rate after drug ± SE | (%) Control | NaCl control rate ± SE | Rate after drug ± SE | (%) Control |
| *d*-Amphetamine | | | | | | |
| 0.10 | 7.3 ± 0.6 | 8.7 ± 1.2[a] | 119 | 4.6 ± 1.0 | 4.9 ± 1.1 | 107 |
| 0.25 | 7.4 ± 0.4 | 10.9 ± 1.2[a] | 147 | 4.3 ± 0.9 | 6.0 ± 0.9[a] | 140 |
| 0.50 | 7.4 ± 0.7 | 13.6 ± 2.3[a] | 184 | 4.1 ± 0.8 | 5.6 ± 0.5[a] | 137 |
| 1.00 | 7.3 ± 0.6 | 17.6 ± 0.6[a] | 241 | 4.4 ± 0.8 | 4.7 ± 0.4 | 107[b] |
| LSD | | | | | | |
| 0.10 | 6.8 ± 0.6 | 7.6 ± 0.8[a] | 112 | 4.6 ± 0.8 | 5.2 ± 0.7 | 113 |
| 0.20 | 6.6 ± 0.5 | 7.1 ± 0.6 | 108 | 4.6 ± 0.9 | 4.7 ± 0.6 | 102 |
| 0.40 | 6.9 ± 0.6 | 6.6 ± 0.5 | 96 | 4.4 ± 1.0 | 2.7 ± 0.3[a] | 61[b] |
| 0.80 | 7.3 ± 0.3 | 6.4 ± 0.5[a] | 88 | 4.5 ± 1.0 | 2.4 ± 0.3[a] | 53[b] |

[a]Statistically different than NaCl control (matched pair $t$ test, $P < 0.05$).

[b]Statistically different than corresponding mean of the Fisher rats ($t$ test, $P < 0.05$).

highest dose (1.0 mg/kg) had no consistent effect on the average response rate. In addition, the largest change from control rate was noted after 1.0 mg/kg given to *F* rats (241% of control), as compared to the 140% of control value observed with the *SD* rats at 0.25 mg/kg of *d*-amphetamine.

LSD produced a significant increase in the overall response rate of *F* rats at 0.10 mg/kg, whereas nonsignificant increases were noted at 0.20 mg/kg for *F* rats and 0.10 and 0.20 mg/kg for *SD* rats. A significant decrease in the average response rate was observed in *SD* rats at 0.40 and 0.80 mg/kg while *F* strain rats were affected significantly at the high dose only.

## DISCUSSION

One of the main findings of this experiment is that *F* strain rats differ from *SD* rats in terms of operant baseline response rates. In the food-reinforced FI 60 sec schedule, *F* rats responded at a lower rate than *SD* rats particularly in the first half of the 60 sec interval. On the other hand, *F* rats responded approximately twice as fast as the *SD* rats on the continuous avoidance schedule. This strain-related difference in avoidance responding is in accord with Barrett *et al.* (1973), who found that *F* rats acquire an active, discriminated Y-maze task more rapidly than random bred *SD* rats.

The *F* strain rats also appeared more sensitive to the behavioral effects of *d*-amphetamine than *SD* rats, and the difference was not predicted from baseline response rates. In the avoidance experiment, *F* strain rats showed greater increases in response rate following *d*-amphetamine than the *SD* rats in spite of the fact that the former group of rats had a baseline rate approximately twice that of the latter group. Although *d*-amphetamine had similar rate-dependent effects on food-reinforced FI responding and resulted in a maximal increase in overall rate of 130% of control for both strains, a comparison of the two dose response curves (Table 2) suggests that *F* rats were affected by *d*-amphetamine more than *SD* rats. That is, both strains of rats showed an inverted U-shaped dose response curve after *d*-amphetamine, but the curve for the *SD* rats appeared displaced to the right. *F* rats were consistently stimulated at low doses and were more sensitive than *SD* rats to the behavioral disruptive effects of higher doses of *d*-amphetamine. Viewed in this perspective, one may conclude that *F* strain rats were more responsive than *SD* rats to the effects of *d*-amphetamine. It is also noteworthy that regression line analysis of successive quartiles of FI responding indicated that *d*-amphetamine produced similar rate-dependent effects in both rat strains. A larger rate-dependent effect (i.e., regression lines with more negative slopes) was predicted for the *F* rats since these subjects consistently responded at a lower rate than the *SD* rats.

Lower doses of LSD increased and higher doses suppressed operant response rates, which is in accord with previously reported data (Jarrard,

1963; Appel, 1971; Tilson and Sparber, 1973). The results of the present experiments also indicate that *SD* rats were more responsive that *F* rats to the behavioral effects of LSD. The FI responding of *SD* rats tended to be increased more by lower doses of LSD, while the continuous avoidance responding of *SD* rats was suppressed more by higher doses of LSD.

In conclusion, the rate-dependent effects of drugs must be interpreted within the context of a plethora of pharmacological, environmental, and organismal variables. In our investigation, it was concluded that *F* strain rats were more sensitive to the behavioral effects of *d*-amphetamine, while *SD* rats were more sensitive to those of LSD. However, strain-related difference in responsiveness to the drugs were not necessarily predicted from their respective baseline rates of responding. Differences in neurotransmitter synthesis and turnover (Rosecrans and Schechter, 1972; Segal *et al.*, 1972) or balance of inhibitory-facilitatory neuronal function (Swonger and Rech, 1972; Rech *et al.*, 1974) between subjects, strain, or even between rats of the same strain from different suppliers (Nakamura and Anderson, 1962), deserve further attention and study by behavioral pharmacologists.

## REFERENCES


Appel, J. B. (1971). Effects of LSD on time-based schedules of reinforcement. *Psychopharmacologia (Berl.)* 21, 174-186.

Barrett, R. J., Leith, N. J., and Ray, O. S. (1973). A behavioral and pharmacological analysis of variables mediating active avoidance behavior in rats. *J. Comp. Physiol. Psychol.* 82, 489-500.

Carey, R. J., and Kritkausky, R. P. (1972). Absence of a response-rate-dependent effect of *d*-amphetamine on a DRL schedule when reinforcement is signalled. *Psychon. Sci.* 26, 285-286.

Evans, H. L., Ghiselli, W. B., and Patton, R. A. (1973). Diurnal rhythm in behavioral effects of methamphetamine, p-chloromethamphetamine and scopolamine. *J. Pharmacol. Exp. Ther.* 186, 10-17.

Geller, I., and Seifter, J. (1960). The effects of meprobamate, barbiturates, *d*-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia (Berl.)* 1, 482-492.

Glick, S. D., and Milloy, S. (1973). Rate-dependent effects of *d*-amphetamine on locomotor activity in mice: Possible relationship to paradoxical amphetamine sedation in minimal brain dysfunction. *Eur. J. Pharmacol.* 24, 266-268.

Hanson, H. M., Witoslawski, J. J., and Campbell, E. H. (1967). Drug effects in squirrel monkeys trained on a multiple schedule with a punishment contingency. *J. Exp. Anal. Behav.* 10, 565-569.

Heffner, T. G., Drawbaugh, R. B., and Zigmond, M. J. (1974). Amphetamine and operant behavior in rats: Relationship between drug effect and control response rate. *J. Comp. Physiol. Psychol.* 86, 1031-1043.

Jarrard, L. E. (1963). Effects of *d*-lysergic acid diethylamide on operant behavior in the rat. *Psychopharmacologia (Berl.)* 5, 39-46.

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

Laties, V., and Weiss, B. (1966). Influence of drugs on behavior controlled by internal and external stimuli. *J. Pharmacol. Exp. Ther.* **152**, 388-396.

Marquis, W. M., Tilson, H. A., and Rech, R. H. (1973). Effects of amphetamine, LSD, psilocybin and DOM on schedule-controlled behavior in the rat. *Fed. Proc.* **32**, 818.

McMillan, D. E. (1973). Drugs and punished responding. I. Rate dependent effects under multiple schedules. *J. Exp. Anal. Behav.* **19**, 133-145.

Nakamura, C., and Anderson, N. (1962). Avoidance behavior differences within and between strains of rats. *J. Comp. Physiol. Psychol.* **55**, 740-747.

Rech, R. H., Tilson, H. A., and Marquis, W. F. (1975). Adaptive changes in behavior after chronic administration of various psychoactive drugs. *In* A. J. Mandel (Ed.), "Neurobiological Mechanisms of Adaptation and Behavior," pp. 263-286. New York: Raven Press.

Rosecrans, J. A., and Schechter, M. D. (1972). Brain 5-hydroxytryptamine correlates of behavior in rats: Strain and sex variability. *Physiol. Behav.* **8**, 503-510.

Segal, D., Kuczenski, R., and Mandell, A. (1972). Strain differences in behavior and brain tyrosine hydroxylase activity. *Behav. Biol.* **7**, 75-81.

Segal, D., Geyer, M., and Weiner, B. (1975). Strain differences during intraventricular infusion of norepinephrine: Possible role of receptor sensitivity. *Science* **189**, 301-303.

Swonger, A. K., and Rech, R. H. (1972). Serotonergic and cholinergic involvement in habituation of activity and spontaneous alternation of rats in a Y-maze. *J. Comp. Physiol. Psychol.* **84**, 509-522.

Thompson, D. M., and Corr, P. B. (1974). Behavioral parameters of drug action: Signalled and response independent reinforcement. *J. Exp. Anal. Behav.* **21**, 151-158.

Tilson, H. A., and Rech, R. H. (1973). Prior drug experience and effects of amphetamine on schedule-controlled behavior. *Pharmacol. Biochem. Behav.* **1**, 129-132.

Tilson, H. A., and Rech, R. H. (1974). The effects of *p*-chlorophenylalanine on morphine analgesia, tolerance and dependence development in two strains of rats. *Psychopharmacologia (Berl.)* **35**, 45-60.

Tilson, H. A. and Sparber, S. B. (1973). Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and *d*-amphetamine on various components of fixed interval responding in the rat. *J. Pharmacol. Exp. Ther.* **184**, 376-384.