Pharmacology Biochemistry & Behavior, Vol. 30, pp. 535–537. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

BRIEF COMMUNICATION

Patterns of Locomotor and Stereotypic Behavior During Continuous Amphetamine Administration in Rats

EILEEN M. HOLLINGSWORTH AND KATHYRNE MUELLER[1]

Psychology Department, Texas Christian University, Fort Worth, TX 76129

Received 6 April 1987

HOLLINGSWORTH, E. M. AND K. MUELLER. *Patterns of locomotor and stereotypic behavior during continuous amphetamine administration in rats.* PHARMACOL BIOCHEM BEHAV 30(2) 535–537, 1988.—The present study examined the behavioral effects of continuous subcutaneous infusion of amphetamine (AMPH) to rats. Saline and 3 AMPH doses were infused for 96 hr (0.2 mg/kg/hr, 0.55 mg/kg/hr, 0.9 mg/kg/hr; n=12). Locomotor behavior, grooming, gnawing and licking, sniffing, and head-bobbing were recorded for each animal for 1 hr in the light cycle and 1 hr in the dark cycle. The low dose AMPH animals exhibited increased locomotor activity. The medium and high dose groups developed similar behavioral patterns consisting of increased grooming and sniffing and changes in circadian rhythms of activity. Although most behaviors exhibited were similar to those discussed in previous literature describing the effects of chronic amphetamine, the pattern of the behaviors was not. Furthermore, continuous administration of AMPH seems to reliably increase the frequency of behaviors which are rarely observed after acute or chronic amphetamine. This finding has important implications since administration of AMPH to rats has been suggested to be an animal model of schizophrenia.

Continuous amphetamine Locomotor behavior Stereotypy Circadian rhythms Self-injurious behavior

AMPHETAMINE (AMPH) models of schizophrenia have been posited because of behavioral and neurochemical similarities between schizophrenics and persons taking high doses of amphetamine [1]. Initially, acute and chronic injections of AMPH to rats were employed as animal models of schizophrenia. However, the behaviors and the neurochemical changes which underlie schizophrenia are thought to be present continuously and thus the model should also be more continuous. Therefore, investigators began developing more continuous modes of AMPH administration. Although acute and chronic AMPH have been extensively studied, continuous modes of administration of AMPH are relatively new.

The behavioral effects of amphetamine have been somewhat specific to the mode of administration. Chronic administration of higher doses (which produce a three-phase response consisting of hyperactivity-stereotypy-hyperactivity) results in an increase in hyperactivity in the third phase [7] and a decrease in licking/biting [3].

Continuous administration of amphetamine with silicone pellets or osmotic pumps increases locomotor activity and stereotypy after about 4 hours; tolerance then develops to these behaviors after several days [6]. Since continuous administration techniques are relatively new, dose-related changes in behavior during continuous administration of AMPH have not been studied nearly as extensively as dose-dependent changes in behavior during chronic administration of AMPH. The present study examines changes in specific behaviors during continuous subcutaneous infusion of three doses of AMPH.

METHOD

Animals

Forty-eight male albino Sprague-Dawley (Harlan-Sprague-Dawley, Indianapolis, IN) rats (300–350 g) were subjects. Animals were divided into four groups (n=12) and were infused for 96 hr with saline (SAL), 0.2 mg/kg/hr AMPH (LOW), 0.55 mg/kg/hr AMPH (MED), or 0.9 mg/kg/hr AMPH (HIGH). The low dose was the smallest dose which produced a behavioral effect, whereas the highest dose was the highest dose of AMPH which could be administered for four continuous days without any deaths.

[1]Requests for reprints should be addressed to Dr. Kathyrne Mueller.

TABLE 1

STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN GROUPS

Locomotions	
Dose	$F(3,44)=3.158$, $p<0.05$
Day of Experiment	$F(3,132)=5.051$, $p<0.01$
Dose × Time of Day	$F(3,44)=5.955$, $p<0.01$
Dose × Day of Experiment	$F(9,132)=4.244$, $p<0.001$
Time of Day × Day of Experiment	$F(3,132)=6.046$, $p<0.01$
Dose × Time of Day × Day of Experiment	$F(9,132)=3.660$, $p<0.001$
Rears	
Time of Day	$F(1,44)=10.282$, $p<0.05$
Dose × Time of Day	$F(3,44)=4.139$, $p<0.05$
Time of Day × Day of Experiment	$F(3,132)=3.735$, $p<0.05$
Grooming	
Dose	$F(3,44)=4.026$, $p<0.05$
Time of Day	$F(1,44)=11.321$, $p<0.01$
Day of Experiment	$F(3,132)=5.063$, $p<0.01$
Dose × Day of Experiment	$F(9,132)=2.043$, $p<0.05$
Gnawing and Licking	
Dose	$F(3,44)=3.260$, $p<0.05$
Sniffing Cage	
Dose	$F(3,44)=9.554$, $p<0.001$
Time of Day	$F(1,44)=8.554$, $p<0.01$
Day of Experiment	$F(3,132)=3.748$, $p<0.01$
Time of Day × Day of Experiment	$F(3,132)=4.178$, $p<0.01$
Dose × Time of Day × Day of Experiment	$F(9,132)=2.62$, $p<0.01$
Head-Bobbing	
Dose	$F(3,44)=4.971$, $p<0.01$
Day of Experiment	$F(3,132)=13.06$, $p<0.001$
Dose × Day of Experiment	$F(9,132)=4.354$, $p<0.001$

Procedure

A stainless steel infusion button (Instech Laboratories) was sutured to the left shoulder muscle of each rat under Nembutal anesthesia. The animals were housed in the test chambers (45.6 ×26×44.5 cm) immediately after surgery and for the duration of the study. Six days later, animals were connected to the infusion pump via a fluid swivel which allowed freedom of movement [2].

Behavior was recorded on videotape for 60 minutes during the 6th hour of the light cycle and the 6th hour of the dark cycle. (These middle periods of the light and dark cycles were chosen to avoid activity changes produced during the transition from one cycle to another.) The following behaviors were recorded: locomotions, rears, grooming, gnawing and licking the cage, sniffing the surface of the cage and head-bobbing. The last four behaviors were expressed as the amount of time the animals engaged in the behaviors for longer than 10 seconds during each daily session.

RESULTS

A repeated measures ANOVA (dose × day × cycle) was used to analyze the behavioral data (see Table 1). The analyses examined dose-related differences across each behavior, however the remainder of the results section is organized to emphasize the differences in patterns of behavioral changes between groups.

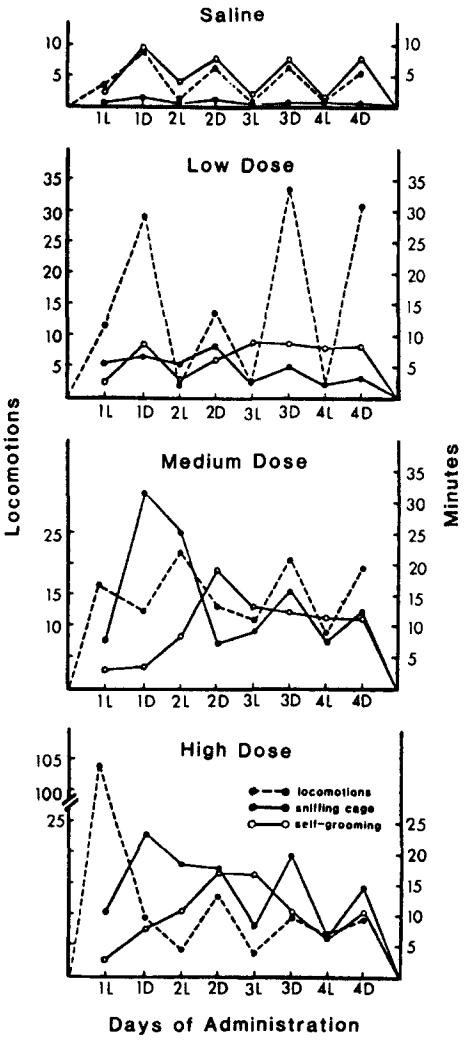

FIG. 1. Behavioral results following continuous infusion of AMPH for 96 hr. The left abscissa represents the number of locomotions. The right abscissa represents the number of minutes engaged in sniffing cage and grooming. (The maximum number of minutes possible for each taped session was 60 min.) The ordinate represents the observation periods, one in the light cycle (L) and one in the dark cycle (D) for each of the 4 days of the experiment.

Saline Group

Saline animals were fairly inactive. As shown in Fig. 1, the well known circadian rhythm in activity was obvious.

Low Dose Group

Low dose animals were more active than saline controls with respect to the behaviors shown in Fig. 1. In general, circadian rhythmicity was maintained. Except for head-bobbing, there was little change in behavior over days. Head-bobbing appeared on the first day of administration, but decreased on day 2 and remained low (data not shown). Gnawing and licking were seldom observed (data not shown). Rears did not change during the four days of infusion (data not shown).

Medium Dose Group

Medium dose animals were more active than low dose

animals with respect to sniffing and grooming, as seen in Fig. 1. There was also an interruption in normal circadian rhythms of activity; during the first two days, more locomotions were exhibited during the light cycle than in the dark cycle. Rhythms of sniffing behavior were also interrupted, although to a lesser degree.

Head-bobbing was present on the first day of administration (mean number of minutes=4.4 for the light and dark cycle combined), but decreased to saline control levels by day 2. Gnawing and licking were seen in 8 of the 12 animals in this group, although for very short durations. (The mean number of minutes engaged in licking/biting was less than 10 minutes during the entire infusion period.) Rearings did not change during the four days of infusion. Two animals exhibited self-injurious behavior.

High Dose Group

Animals in the high dose group were about as active as medium dose animals (see Fig. 1). Locomotion was dramatically increased following the first 12 hours of infusion, but tolerance developed by 24 hours. Sniffing and groming were also elevated to about the same levels as the medium dose group. Circadian rhythmicity was interrupted during the first two days.

The pattern of head-bobbing observed was basically the same as seen with the low and medium dose animals. As with the medium dose group, some gnawing and licking was observed, but with fewer animals for longer durations. Rearings did not change during the infusion period. Self-injurious behavior was present in 3 animals in this group.

DISCUSSION

Behavior patterns produced by low doses of continuous AMPH were similar to those produced by acute and chronic injections. However, at higher doses the patterns began to differ. Much less stereotypy was observed than has been reported with acute and chronic AMPH. On the other hand, two behaviors which are rarely produced by acute and chronic AMPH were observed after continuous AMPH—grooming and self-injurious behavior. Continuous amphetamine also produced an interruption in circadian rhythms of activity of the medium and high dose animals.

The low dose group showed high levels of locomotion with very little change in any other behavior. The pattern is the same as that produced by chronic administration of low doses of AMPH [7]. Medium and high dose animals also remained hyperactive with respect to saline controls throughout the study.

Stereotypic gnawing and licking or head-bobbing were rarely observed even in the high dose group. Unfortunately, comparisons are difficult to make between these data and reported data from AMPH pellets or minipumps. In the latter studies, gnawing and licking, sniffing, and grooming scores were sometimes reported as a single cumulative stereotypy score (cf. [4]). Such a procedure tends to inflate the amount of stereotypy exhibited at any one time, and can also obscure different patterns of tolerance/sensitization for the various behavioral components of stereotypy.

Sniffing the cage and grooming were the behaviors most often observed in the present experiment. Both medium and high dose groups groomed more than saline controls throughout the study. Acute and chronic administration of AMPH generally eliminates grooming [7]. Therefore, the appearance of excessive grooming during continuous administration of higher doses of AMPH represents an important discrepancy between the behavioral effects of different modes of administration of AMPH. Increases in grooming have also been reported in animals implanted with AMPH pellets [5].

Two animals in the medium dose group and three in the high dose group exhibited self-injurious behavior. Self-injurious behavior has relatively consistently been observed in animals implanted with AMPH pellets [5,6], but is rarely produced by acute or chronic AMPH. Therefore, self-injurious behavior also seems to be somewhat dependent on the mode of administration of AMPH.

One interesting finding not reported in earlier literature is the disruption of circadian rhythms of activity during continuous AMPH. Of course, one might expect continuous amphetamine to interfere with sleep and therefore to obscure the usual differences between activity levels during the light and dark cycles. However, in this experiment the higher doses of AMPH reversed the normal behavioral rhythm; animals exhibited more activity during the light cycle than during the dark cycle.

If one is to accept the idea of an animal AMPH model of schizophrenia, one must seriously address the question of which mode of administration of AMPH is most appropriate.

ACKNOWLEDGEMENTS

This research was conducted as partial fulfillment of the Masters of Science degree in the department of Psychology. The authors thank Steven Travelbee for assistance.

REFERENCES

1. Bell, D. S. Comparison of amphetamine psychosis and schizophrenia. Br. J. Psychiatry 111:701–707; 1965.
2. Brown, Z. W.; Amit, Z.; Weeks, J. R. Simple flow-thru swivel for infusions into unrestrained animals. Pharmacol. Biochem. Behav. 5:363–365; 1976.
3. Eichler, A. J.; Antelman, S. M.; Black, C. A. Amphetamine stereotypy is not a homogenous phenomenon: Sniffing and licking show distinct profiles of sensitization and tolerance. Psychopharmacology (Berlin) 68:287–290; 1980.
4. Eison, M. S.; Eison, A. A.; Iversen, S. Two routes of amphetamine administration induce different behavioral and neurochemical effects in the rat. Neurosci. Lett. 39:313–319; 1983.
5. Mueller, K.; Saboda, S.; Palmour, R.; Nyhan, W. L. Self-injurious behavior produced in rats by daily caffeine and continuous amphetamine. Pharmacol. Biochem Behav. 17:613–617; 1982.
6. Nielsen, E. B.; Lee, T. H.; Ellison, G. Following several days of continuous administration d-amphetamine acquires hallucinogen-like properties. Psychopharmacology (Berlin) 68:197–200; 1980.
7. Segal, D. S.; Mandell, A. J. Long-term administration of d-amphetamine: Progressive augmentation of motor activity and stereotypy. Pharmacol. Biochem. Behav. 2:249–255; 1974.