Pharmacology Biochemistry and Behavior, Vol. 2, pp. 503–508. ANKHO International Inc., 1974. Printed in the U.S.A.

Tolerance Development to Chronic Methamphetamine Intoxication in the Rhesus Monkey[1, 2, 3]

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(Received 30 November 1973)

FISCHMAN, M. W. AND C. R. SCHUSTER. *Tolerance development to chronic methamphetamine intoxication in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 2(4) 503–508, 1974. – The effects of the chronic administration of methamphetamine on food- and water-reinforced responding were investigated in the rhesus monkey. These animals received one infusion of d-methamphetamine HCl every three hours, eight times daily in doses starting at 0.0625 mg/kg/infusion and gradually increasing to 6.5 mg/kg/infusion. The effects of this drug regimen on food- and water-reinforced behavior generated by independent fixed-ratio 10 schedules of reinforcement were studied. Tolerance developed to the physiologically and behaviorally toxic effects of the drug over a six to ten month period. Gross morphological changes were not seen at necropsy nor during examination of brain, heart, liver or kidney tissue under light microscopy.

Methamphetamine Chronic drug administration Fixed-ratio Tolerance Rhesus monkey

RESEARCH on the effects of the amphetamines has primarily utilized paradigms in which the drug was administered either acutely or on an interrupted chronic basis with 5–10 infusions weekly for several weeks or months [18]. In these studies, no attempt was made to maintain constant drug levels in the blood, and it is possible that many of the toxic effects seen could be due to the changing levels of drug in the body. Both physiological and behavioral toxicity have been reported after amphetamine administration. To date, only a few studies have investigated the possiblity that morphological changes might be induced by frequent administration of these drugs. The primary pathology noted thus far is the presence of petechial hemorrhages on the surface of the brain in cats [8], rabbits [15] and rhesus monkeys [8,26]. In addition, Escalante and Ellinwood [8] have reported structural changes in some reticular neurons in the medulla and pons of the cat after methamphetamine was administered on an interrupted chronic regimen. Observational measures of behavior have been in accord in reporting the appearance of stereotyped behavior patterns after either acute or interrupted chronic administration of this family of drugs. These repetitive behavior patterns, their form unique to each species, have been seen in rodents [25], cats [7], squirrel monkeys [25], rhesus monkeys [6], and chimpanzees [10]. In addition, comparable behavior patterns have been described in humans who chronically abuse amphetamines [5].

A major effect noted after long-term administration of

[1] This research was supported by USPHS Grants MH-19,732 (W. Richter, Principal Investigator), DA-00250 (D. X. Freedman, Principal Investigator). C. R. Schuster is the recipient of Career Award MH-11,042.

[2] Morphological analysis was conducted by Ward R. Richter, D. V. M., Associate Professor of Pathology, University of Chicago, Pritzker School of Medicine.

[3] d-Methamphetamine HCl was graciously supplied by Abbott Laboratories, North Chicago, Illinois.

amphetamines has been tolerance to their anorexic, euphoric and behavior-disrupting effects [1, 19, 20, 29]. The behavioral tolerance, however, appears to develop selectively. Schuster and Zimmerman [29] for example, reported that the behavioral toxicity seen in rats receiving amphetamine and responding on an appetitive operant task dissipated over time. Tormey and Lasagna [31] however, while corroborating this behavioral tolerance in rats responding for food reinforcement, showed that large increases in general activity level do not return to predrug levels in parallel with the tolerance development seen in food-reinforced behavior. It has been suggested that the development of behavioral tolerance is dependent on the reinforcement contingencies of the task being studied, and thus will be seen when the drug disrupts behavior such that the reinforcement requirements are no longer being met [27]. An analysis of this type of tolerance development has not been made in the rhesus monkey.

A major unanswered question is whether the chronic administration of the amphetamines produces correlated functional and organic changes. The present study was designed to investigate the effects of chronically administered d-methamphetamine on responding under fixed-ratio (FR) schedules of reinforcement in the rhesus monkey, and to correlate these effects with any morphological changes which might be found. Initially, the acute effects of a range of doses of d-methamphetamine on food and water-reinforced behavior were determined. These results were then used as the bases for examining responding reinforced by food and water in rhesus monkeys chronically maintained on doses of d-methamphetamine ranging from 0.5 mg/kg/day to 52.0 mg/kg/day. At the completion of the behavioral studies, necropsies were performed and all animals were examined for signs of morphological changes.

METHOD

Animals

Eight healthy adult male rhesus monkeys, weighing between 4.0 and 6.0 kg, with no prior drug or experimental histories were used for this experiment.

Apparatus

All animals were housed individually in sound-attenuated cubicles 83 cm deep, 67 cm wide and 75 cm high. The ceiling was white translucent Plexiglas covering a houselight, and there was a pan containing sawdust beneath the grid floor. The door was equipped with a food dish beneath a hole through which food pellets (1 g Noyes Formula L Monkey Pellets) could be delivered via a pellet dispenser (Gerbrands Model G 5210) and a small peephole for observing the monkey without disturbance. Two levers (LVE 121-07) were also mounted on the door, each beneath a rectangular piece of Plexiglas which could be transilluminated by stimulus lights. Four of the cubicles were equipped with standard drinking tubes through which water could be obtained during the experimental session. Stainless steel reservoirs, through which 1 ml of water could be delivered, were mounted in the other four cubicles. The water gradually emptied into a collection bottle if the animal did not drink it within 1–2 sec. The monkeys, wearing stainless steel harnesses, were restrained only by an 18-in. long stainless steel flexible spring arm attached at one end to the harness and at the other end to the middle of the back wall of the cubicle [28,32].

Procedure

The animals were allowed to adapt to the experimental cubicles for one week during which time they were fed 120 g of Noyes monkey pellets daily and trained to drink from their water delivery system. Following adaptation, they were placed on 22 hr food and water deprivation. During the remaining two hours, houselights and lever lights were illuminated and daily food (for all monkeys) and water (for 4 monkeys) rations were contingent on independent fixed-ratio 10 schedules of reinforcement (FR 10; ten responses for one reinforcement). Food pellets delivered but not consumed were counted at the end of each experimental session. The other four monkeys had water freely available during the two-hour experimental session. Experimental sessions were conducted seven days/week.

When daily food and water intake showed stable values over one week, a chronic intravenous catheter was surgically implanted. Under pentobarbital anesthesia, a silicone catheter was inserted into the internal jugular vein and threaded subcutaneously over the right shoulder to a point in the midback where it exited via a puncture wound. From there it ran through the spring restraining arm and out the back of the cubicle, through a peristaltic pump (Cole-Parmer 7540X) to a drug bottle.

The acute drug regimen. Following the catheter implantation, two animals received infusions of 1 ml of saline every three hours, eight times per day throughout this experiment. After responding again stabilized under the FR schedules of food and water reinforcement, d-methamphetamine was administered intravenously at one week intervals, five minutes prior to an experimental session. The test doses, specified in terms of the hydrochloride salt, dissolved in 0.9% physiological saline, and infused in a 1 ml volume, were: 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg. They were administered both in an ascending and descending series.

The chronic drug regimen. Six animals were placed on the chronic drug regimen in which 1 ml of d-methamphetamine was delivered intravenously every three hours eight times daily. The temporal relation between each drug infusion and the start of the experimental session was constant for each animal but varied between animals. The initial dose of 0.0625 ml/kg/infusion (0.5 mg/kg/day) was administered until responding on the FR 10 schedule of food reinforcement either reached the pre-operative baseline levels or a new stable baseline. For five animals, the methamphetamine dose was then increased to 0.125 mg/kg/infusion (1.0 mg/kg/day), 0.25 mg/kg/infusion (2.0 mg/kg/day), 0.5 mg/kg/infusion (4.0 mg/kg/day), 0.75 mg/kg/infusion (6.0 mg/kg/day) and so on, in increments of 0.25 mg/kg/infusion until a severely debilitating dose was reached to which no behavioral tolerance developed. At such a dose, the animal was too weak to press the lever and showed complete suppression of all responding for more than one week. For one animal, at doses above 1.0 mg/kg/infusion, the doses were increased in 1.0 mg/kg increments. Animals received each dose of d-methamphetamine for varying periods of time depending on the rate of tolerance development. The number of days spent at each dose ranged from 3–40. When a dose was

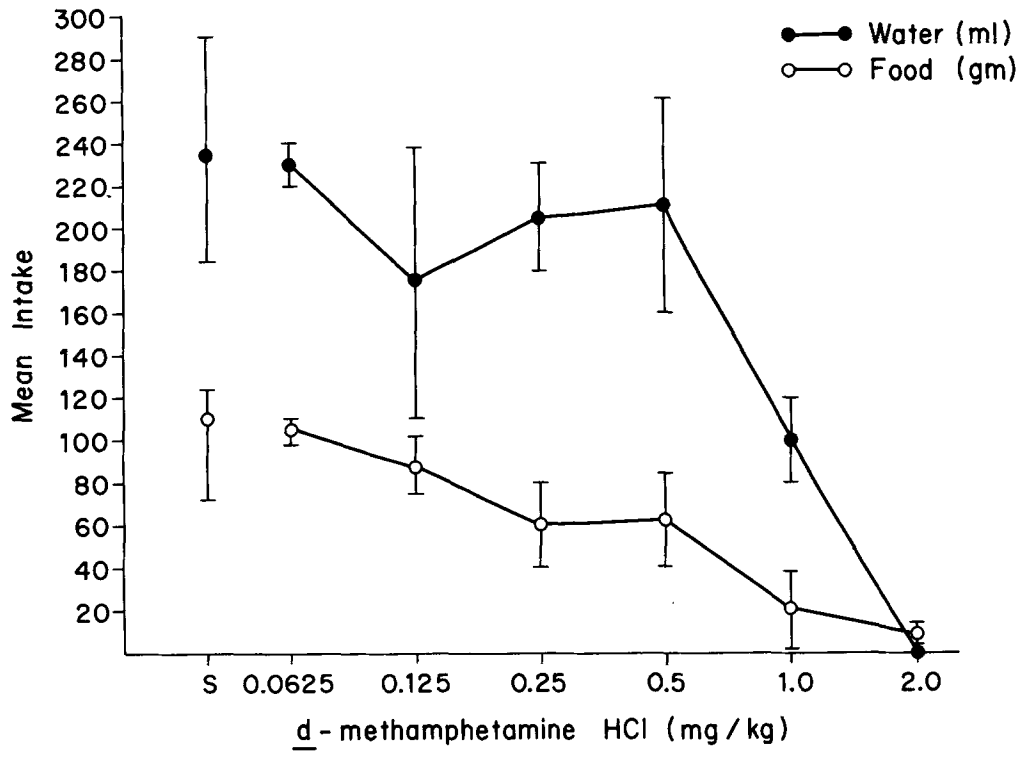

FIG. 1. Dose response curves of mean food and water intake for two monkeys after acute intravenous infusions of d-methamphetamine HCl ranging in concentration from 0.0625 mg/kg to 2.0 mg/kg. Points labelled 'S' represent a mean of five days on the saline condition for each of the two animals; brackets through the points indicate the range over those five days. Water intake (in ml) is shown by the closed circles; open circles indicate food intake (in g). Brackets through these points indicate the range in intake for each dose of the drug.

reached to which no behavioral tolerance developed, the animal was sacrificed under deep pentobarbital anesthesia, and a necropsy performed.

Necropsy. A complete postmortem examination was performed and tissues were collected for light microscopic evaluation. These included brain, spinal cord, trachea, esophagus, lungs, heart, aorta, stomach, small intestine, colon, liver, spleen, kidney, urinary bladder, thyroids, adrenal pituitary, gonads, bone, bone marrow, skeletal muscle and skin. They were immersed in 10% buffered Formalin, embedded in paraffin and fixed with hematoxylin and eosin prior to microscopic examination.

RESULTS

The acute drug regimen. Although 0.0625 mg/kg of d-methamphetamine did not have an effect on either food or water intake, doses of 0.25 mg/kg and above depressed food-reinforced responding; at doses of 1.0 and 2.0 mg/kg of this drug, food-reinforced responding was virtually eliminated (Fig. 1). Both animals showed decreased water intake with increases in drug dose, although this measure showed more variability than food intake. However, with doses of 1.0 and 2.0 mg/kg of methamphetamine, water intake was reduced to at least 43% of the saline control level. In addition, it was found that any food- or water-reinforced responding seen after 1.0 and 2.0 mg/kg of drug occurred at the beginning of the session, and postreinforcement pauses were considerably longer. Drug-induced decrements in responding for food and water occurred only on the day that drug was administered. Responding was always recovered by the following day when neither suppressed rates nor a rebound effect were seen.

The chronic drug regimen. The chronic administration of d-methamphetamine had, in general, an initial suppressant effect on responding under the FR 10 schedule of food presentation. Data, showing the mean percent change from baseline food intake, are presented in Fig. 2. The suppressant effect is observable on the first day of a new dose level of methamphetamine. By the last day at each level, however, the development of some tolerance to the drug can be seen in the return of food-reinforced responding to saline control levels. For some animals, a return to predrug baseline rates did not occur at the lower drug levels, although responding increased considerably relative to the rates seen on the first day at that dose. When a new stable baseline rate was reached, the drug dose was increased. As the chronic regimen continued and the dose was raised, there was a return to baseline response rates. The direction of change in intake (from lower to higher levels) from the first to the last day at each dose level was significant in all animals ($p<0.05$). It is clear that tolerance to at least the suppressant and possibly the anorexic effects of the drug developed in these animals. In addition to the development

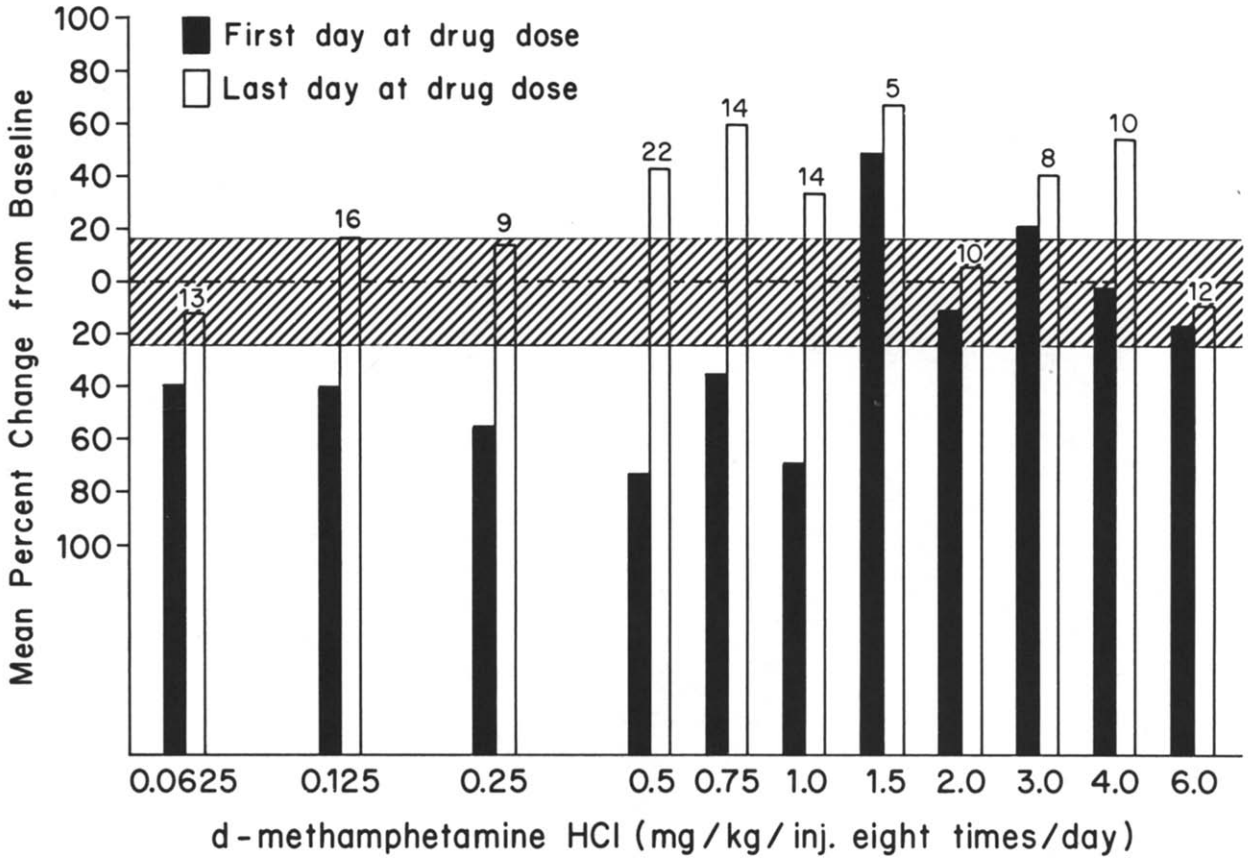

FIG. 2. The effect of chronic methamphetamine administration on fixed-ratio responding for food reinforcement. Mean percent change from baseline is shown as a function of dose of d-methamphetamine HCl administered eight times daily on the chronic drug regimen for six animals. Baseline represents a mean of five days data collected prior to beginning drug administration; the shaded area represents the range over those five days. The first day at each drug dose is indicated by the black bar; the open bar shows data collected on the last day at each drug dose. The number above each open bar is the mean number of days at each of the doses shown.

of a wtihin-dose tolerance, it can also be seen that the tolerance developed to increases in drug dose. That is, the animals were generally most severely affected at the lower drug levels. Increases in the dose of methamphetamine above 1.0 mg/kg/infusion did not continue to result in a consistent decrease in the rate of food-reinforced responding for any of the animals tested, until the final toxic dose was reached. It has often been reported that rate of responding on schedules that engender high response rates (e.g., FR 10) is reduced by amphetamines [3, 13, 21]. This decrease in high rates was seen with the lower unit doses of methamphetamine. However, as tolerance developed and the doses of the drug were increased, rate returned to baseline control values, and for many of the animals actually increased. This increase in response rate occurred with the development of tolerance and often persisted for several weeks.

The water intake data were too variable to permit any statistical analysis. This probably can be attributed to the methods employed to measure it. When a reservoir delivery system was used, the measure of water intake was easily confounded by the animal's hyperactivity, inability to get to the reservoir on time, etc. This failure to get to the reservoir fast enough to consume the reinforcement has also been noted by Segal [30] studying the effects of amphetamine in rats. In addition, when the monkeys were required to suck water through a tube and stable levels of water intake were attained prior to drug, changes in drinking behavior occurred during the chronic regimen such that the monkeys were unable to obtain sufficient water to sustain life. Standard laboratory water bottles were substituted at this time.

In addition to the development of tolerance to the anorexic and response-suppressant effects of chroncially infused d-methamphetamine, the monkeys in this study also showed tolerance to the lethal effects of the drug. Acute doses of d-methamphetamine HCl above 3.0 mg/kg are clearly highly toxic, and have been shown to be fatal to rhesus monkeys when administered intravenously [9]. Therefore the total daily doses reached at the end of the regimen, ranging as high as 52 mg/kg would have been lethal to a non-tolerant animal.

Gross behavioral observations. At drug levels between approximately 0.5 mg/kg/infusion and 1.25 mg/kg/infusion,

all animals showed bizarre repetitive behavior patterns which often initially interfered with efficient performance of the reinforced operants. The animals were extremely hyperactive and spent large blocks of time picking on small areas of their bodies. These animals were very similar to those described by Ellinwood [6] after chronic methamphetamine intoxication. This exaggerated grooming behavior would often continue for days at a time, ceasing only during the 2-hr daily experimental session. During the time when this repetitive abnormal behavior was most evident, animals did not respond to external stimuli, such as loud noises or the presence of the experimenter, but as soon as the stimulus signalling the start of the experimental session appeared, the animals would immediately begin responding appropriately on the lever. With increases in drug dose, and continued time on the chronic drug regimen, most of the stereotypic behavior disappeared, although some hyperactivity persisted for the duration of the experiment.

Morphological observations. No gross morphological changes were detected in these animals during the complete necropsy performed immediately after they were sacrificed. In additon, light microscopic examination of tissues collected during necropsy failed to reveal any abnormal changes.

DISCUSSION

The major finding in this study is the development of behavioral and physiological tolerance to doses of d-methamphetamine that would be lethal to a monkey never before injected with this drug. Although their behavior was severely disrupted initially, not only were these monkeys eating and drinking normal amounts within a relatively short period of time, but their responding under the FR 10 schedule of food reinforcement also returned to control levels. Only at total daily doses which differed for each monkey, but ranged between 24.0 and 52.0 mg/kg of drug did the monkeys show severe physical debilitation and an inability to continue lever pressing. It was at this point that they were sacrificed. A significant feature of this research was the uninterrupted intravenous administration of d-methamphetamine every 3 hr eight times daily for the duration of the study.

The absence of gross pathological changes in the monkeys in this study after chronic methamphetamine intoxication is in contrast to the vascular changes that have been reported in rabbits [15], monkeys [8,26], and humans [2] after varying periods of time on methamphetamine. It is probable that the regimen followed in this study, in which animals were allowed to become tolerant prior to an increase in dose, afforded some protection and avoided some of the morphological changes observed in these other studies. It is possible that transient lesions do occur and are repaired without any residual evidence in the animals receiving the drug chronically. Further, the contributions of the fillers and binders in the ground-up tablets [26], and other drugs, infections, etc. in the clinical study [2] have not yet been assessed.

The behavioral effects seen on the chronic drug regimen were very different from those seen when the drug was administered acutely. Prior to the chronic administration of methamphetamine, acute infusions of the drug suppressed responding for food and water on an FR 10 schedule of reinforcement at a unit dose of 1.0–2.0 mg/kg, while lower doses had virtually no effect. In contrast, the lower doses of methamphetamine, when chronically administered, had a suppressant effect on responding for food much like the effects on high response rates reported by other investigators studying amphetamine-behavior interactions [16, 21, 23]. At the higher doses (above 8.0 mg/kg/day) a behavioral tolerance developed such that the reduced response rate was not seen. In fact, responding for food often occurred at rates considerably above the saline control levels. This increase in rate was not merely a reflection of non-specific hyperactivity since the food pellets delivered were always consumed. The increase in food intake seen at the middle range of methamphetamine doses cannot be discussed simply as a rebound phenomenon following decreased food intake. One would expect, in fact, to see impaired food intake after a period of semi-starvation [14]. The added food could, however, reflect normal growth in these animals; the intake increases seen here conform quite well with those recently reported by Hamilton [11] studying food intake in normal rhesus monkeys over a period of several years. The possibility exists that the method of raising drug dose on the chronic regimen masked the appearance of a polyphagia at the higher chronic doses. That is, a higher dose of methamphetamine was administered whenever responding for food stabilized near or above baseline levels. If drug doses had not been raised above 1.0–1.5 mg/kg/infusion, for example, food intake may have continued the generally rising trend seen in Fig. 2. A more pronounced hyperphagia after long-term administration of high doses of amphetamines has been reported by Seevers, Ganz, and Deneau (unpublished), indicating why clinical reports on the long-term intake of the amphetamines have shown it to be so ineffective in the control of obesity due to overeating [24]. This tolerance after chronic exposure to large doses of methamphetamine was also correlated with a development of tolerance to the sympathomimetic and lethal effects of the drug, corroborating earlier reports by Harrison *et al.* [22] and Seevers *et al.* (unpublished).

Despite the phenomenal tolerance shown to methamphetamine on the FR 10 schedule with food as the reinforcer, the animals outside of the experimental session behaved in a highly abnormal fashion at the middle range of drug doses (approximately 0.5 mg/kg/infusion to approximately 1.25 mg/kg/infusion). Continuously repetitive behavior after moderately high doses of amphetamine has been observed in rats [22], cats [5,], monkeys [6,17], chimpanzees [10] and humans [4,19]. The constant picking and grooming behvior, limited to restricted areas of the body is particularly common in caged monkeys maintained on amphetamines [6, 25]. It is important to note that this abnormal behavior continued during the 22-hr timeout from the experimental session long after the animals exhibited tolerance to the anorexic and response suppressant effects of the drug, reminiscent of the selective tolerance to the effects of amphetamine reported by Tormey and Lasagna [31], Schuster and Zimmerman [29] and Schuster *et al.* [27]. Behavioral tolerance developed most rapidly to the toxic effects of the drug which interfered with meeting the reinforcement requirements (i.e., a decreased response rate on the FR 10 schedule for food). On the other hand, behavior outside of the experimental session was not under contingency control, and persisted in an abnormal form for a considerably longer period of time. However, even this repetitive behavior tended to disappear as the dose level continued to increase, although some hyperactivity and hyperexcitability were still evident at

doses of 3.0 and 4.0 mg/kg/infusion. Thus, the tolerance, although present, developed selectively. It first appeared in behavior under strict stimulus control, and only later appeared as a general phenomenon, covering many aspects of the monkeys' behavior.

REFERENCES

1. Carlton, P. L. and D. L. Wolgin. Contingent tolerance to the anorexigenic effects of amphetamine. *Physiol. Behav.* **7:** 221–223, 1971.
2. Citron, B. P., M. Halpern, M. McCarron, G. D. Lundberg, R. McCormick, I. J. Pincus, D. Tatter and B. J. Haverback. Necrotizing angiitis associated with drug abuse. *New Engl. J. Med.* **283:** 1003–1011, 1970.
3. Dews, P. B. Studies on behavior. IV. Stimulant action of methamphetamine. *J. Pharmac. exp. Ther.* **122:** 137–147, 1958.
4. Ellinwood, E. H. Amphetamine psychosis. I. Description of the individuals and process. *J. nerv. ment. Dis.* **144:** 273–283, 1967.
5. Ellinwood, E. H. Amphetamine psychosis. A multidimensional process. *Seminars Psychiat.* **1:** 137–147, 1958.
6. Ellinwood, E. H. Effect of chronic methamphetamine intoxication in rhesus monkeys. *Biol. Psychiat.* **3:** 25–32, 1971.
7. Ellinwood, E. H. and O. D. Escalante. Behavior and histopathological findings during chronic methedrine intoxication. *J. Soc. Biol. Psychiat.* **2:** 27–39, 1970.
8. Escalante, O. D. and E. H. Ellinwood. Effects of chronic amphetamine intoxication in adrenergic and cholinergic structures in the central nervous system: Histochemical observations in cats and monkeys. In: *Current Concepts on Amphetamine Abuse.* Dept. of Health, Education and Welfare Publication No. 72-9085, 1972, pp. 97–106.
9. Fischman, M. W. and C. R. Schuster. Behavioral toxicity of chronic methamphetamine in the rhesus monkey. In: *Behavioral Toxicology,* edited by B. Weiss and V. Laties. New York: Plenum Publ. Corp, in press.
10. Fitz-Gerald, F. Effects of d-amphetamine upon behavior of young chimpanzees reared under different conditions. In: *Neuropsychopharmacology,* edited by H. Brill and J. Cole. Vol. 5. Amsterdam: Elsevier, 1967, p. 1226.
11. Hamilton, C. L. Long-term control of food intake in the monkey. *Physiol. Behav.* **9:** 1–6, 1972.
12. Harrisson, J. W. E., C. M. Ambrus and J. L. Ambrus. Tolerance of rats toward amphetamine and methamphetamine. *J. Am. pharm. Ass.* **41:** 539–541, 1952.
13. Hearst, E. and J. R. Vane. Some effects of d-amphetamine on the behavior of pigeons under intermittent reinforcement. *Psychopharmacologia* **12:** 58–67, 1967.
14. Kalant, H., A. E. LeBlanc and R. J. Gibbins. Tolerance to and dependence on, some non-opiate psychotropic drugs. *Pharmac. Rev.* **23:** 135–191, 1971.
15. Kasirsky, G., I. H. Zaidi and M. F. Tansy. LD50 and pathologic effects of acute and chronic administration of methamphetamine HCl in rabbits. *Res. Communs. chem. Pathol. Pharmac.* **3:** 215–231, 1972.
16. Kelleher, R. T. and L. Cook. Effects of d-amphetamine, meprobamate, phenobarbital, mephensin or chlorpromazine on DRL and FR schedules of reinforcement with rats. *J. exp. Analysis Behav.* **2:** 267, 1959.
17. Kjellberg, B. and A. Randrup. Stereotypy with selective stimulation of certain items of behavior observed in amphetamine-treated monkeys (Cercopithecus). *Pharmakopsychiatrie* **5:** 1–12, 1972.
18. Kosman, M. E. and K. R. Unna. Effects of chronic administration of the amphetamines and other stimulants on behavior. *J. clin. Pharmac. Ther.* **9:** 240–254, 1968.
19. Kramer, J. C., V. S. Fischman and D. C. Littlefield. Amphetamine Abuse. *J. Am. med. Ass.* **201:** 305–309, 1967.
20. Lewander, T. A mechanism for the development of tolerance to amphetamine in rats. *Psychopharmacologia* **21:** 17–31, 1971.
21. McMillan, D. E. Effects of d-amphetamine on performance under several parameters of multiple fixed ratio, fixed interval schedules. *J. Pharmac. exp. Ther.* **167:** 26–33, 1969.
22. Munkvad, I. and A. Randrup. The persistence of amphetamine stereotypes of rats in spite of strong sedation. *Acta psychiat. scand.* Suppl. 191, **42:** 178–186, 1966.
23. Owen, J. E., Jr. The influence of dl-, d- and l-amphetamine and d-methamphetamine on a fixed-ratio schedule. *J. exp. Analysis Behav.* **3:** 293–310, 1960.
24. Penick, S. B. Amphetamines in obesity. *Seminars Psychiat.* **1:** 144–162, 1969.
25. Randrup, A. and I. Munkvad. Behavioral toxicity of amphetamines studied in animal experiments. (Proceedings of the 12th meeting of the European Society for Study of Drug Toxicity, 1970.) *Excerpta Med. Int. Congr. Ser.* **220:** 6–17, 1970.
26. Rumbaugh, C. L., R. t. Bergeron, R. L. Scanlan, J. S. Teal, H. D. Segall, H. C. H. Fang and R. McCormick. Cerebral vascular changes secondary to amphetamine abuse in the experimental animal. *Radiology* **101:** 345–351, 1971.
27. Schuster, C., W. Dockens and J. Woods. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia* **9:** 170–182, 1966.
28. Schuster, C. R. and C. E. Johanson. The use of animal models for the study of drug dependence. In: *Research Advances in Alcohol and Drug Problems,* edited by R. J. Gibbons. New York: Wiley and Sons, Inc., 1974.
29. Schuster, C. R. and J. Zimmerman. Timing behavior during prolonged treatment with d, l-amphetamine. *J. exp. Analysis Behav.* **4:** 327–330, 1961.
30. Segal, E. F. Effects of dl-amphetamine under concurrent VI DRL reinforcement. *J. exp. Analysis Behav.* **5:** 105–112, 1962.
31. Tormey, J. and L. Lasagna. Relation of thyroid function to acute and chronic effects of amphetamine in the rat. *J. Pharmac. exp. Ther.* **128:** 201–209, 1960.
32. Yanagita, T., G. A. Deneau and M. H. Seevers. Evaluation of pharmacologic agents in the monkey by long term intravenous self or programmed administration. *Excerpta Med. Int. Congr. Ser.* **87:** 453, 1965.