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Sensitivity Changes to Dopaminergic Agents in Fine Motor Control of Rhesus Monkeys After Repeated Methamphetamine Administration[1]

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ANDO, K., C. E. JOHANSON, L. S. SEIDEN AND C. R. SCHUSTER. *Sensitivity changes to dopaminergic agents in fine motor control of rhesus monkeys after repeated methamphetamine administration.* PHARMACOL BIOCHEM BEHAV 22(5) 737–743, 1985.—Long-term behavioral and neurochemical effects of repeated methamphetamine (MA) administration were investigated in rhesus monkeys trained to perform a fine motor task requiring control of exerted force for a specified time. Rhesus monkeys were trained to extend their arms into a tube to press a lever with a force between 25 and 40 g for 5 sec in order to receive 1.5 ml of water. The effects of intramuscular administration of MA, apomorphine (APO) and haloperidol (HAL) on responding were compared before and after a 2-week period of repeated MA administration. During this period, MA was given in 4 divided doses starting at a total daily dose of 4 mg/kg/day and increasing to 40 mg/kg/day. Tolerance to MA, increased sensitivity to HAL and no consistent sensitivity change to APO were observed when dose-response functions were redetermined starting 1 month after the repeated MA administration. One month after these determinations were completed, the brains of the monkeys were analyzed for changes in monoamines. Significant depletions of dopamine in the caudate nucleus and serotonin in the frontal cortex were seen. It is hypothesized that the sensitivity changes to the drugs on performance were related to the dopamine depletion.

Methamphetamine Apomorphine Haloperidol Force lever performance Rhesus monkeys
Dopamine depletion Tolerance Supersensitivity

SINGLE administrations of amphetamine and related psychomotor stimulant drugs at low doses generally increase spontaneous motor activity and low rates of responding maintained under intermittent schedules of reinforcement in animals. At high doses, these drugs produce species-characteristic stereotyped behaviors and decrease rates of operant responding. Further increases in dose result in convulsions, coma, and death [18,22]. The repeated administration of psychomotor stimulant drugs has been reported to produce increased sensitivity or tolerance to the drugs depending on the dose and the type of behavior monitored. An increase in sensitivity has been reported for the effects of these drugs on locomotor activity and stereotypy [12, 15, 23]. On the other hand, tolerance has been observed to the hyperthermic, anorectic, cardiovascular, and toxic effects [18] as well as to some of the effects on schedule-controlled [5,7] and self-stimulation behavior [13,14]. Tolerance has also been reported for the discriminative stimulus [1] and reinforcing [17] properties of amphetamines. In addition to these behavioral and physiological changes, the repeated administration of the amphetamines results in long-lasting changes in regional brain monoamine levels. For instance, depletions of dopamine in the caudate nucleus and serotonin in the frontal cortex have been observed in rodents and rhesus monkeys following repeated methamphetamine (MA) administration [6, 20, 24, 27]. Based on uptake studies, it has also been reported that the number of dopamine uptake sites were decreased following MA. However, there were no changes in uptake or in the number or affinity of ^{3}H spiroperidol binding sites [25,26]. In addition to these neurochemical changes, morphologic studies have demonstrated the degeneration of dopamine neuron terminals in the cau-

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date nucleus following a period of repeated MA [2,20]. Other studies have shown that dopamine depletion in the basal ganglia produced by repeated MA administration or 6-hydroxydopamine lesions is correlated with motor dysfunctions [10]. In addition, Parkinson's disease is associated with dopamine deficiency in the brain, and biochemical manipulations that increase dopamine stores improve the motor dysfunctions characteristic of this disease [9]. These observations suggest that repeated MA treatment may alter motor function as a result of its effect on the dopamine system in areas mediating motor control [8].

The purpose of the present experiment was to study sensitivity changes to the effects of MA, apomorphine (APO) and haloperidol (HAL) on a fine motor task requiring control of exerted force in rhesus monkeys after a period of repeated MA administration designed to deplete dopamine. In order to observe whether dopamine depletion had occurred as a result of the repeated MA administration, regional brain monoamine levels in the monkeys were compared to those of non-treated controls. The results demonstrated that repeated MA administration that depleted caudate dopamine levels resulted in tolerance to MA, supersensitivity to HAL and inconsistent changes with APO on fine motor control performance.

METHOD

Animals

Four adult female rhesus monkeys were used. They were experimentally naive and weighed between 4.2 and 4.7 kg at the beginning of the experiment. Each monkey was housed individually in a metal cage (62×70×60 cm) in a room which housed 10 to 15 other monkeys and was fed 100 g of monkey chow (Ralston Purina Co., No. 5038, St. Louis, MO) daily at least 1 hr prior to the experimental session. Each monkey's total daily water intake was restricted to between 135 and 150 ml so that consistent responding was maintained without dehydration. During an experimental session, a maximum of 75 ml of water was available. The remainder of each monkey's daily allotment of water was given in the home cage after the session. When experimental sessions were not conducted, each monkey was given access to 150 ml of water and 100 g of chow in their home cage. Several sugar cubes saturated with liquid vitamins were also given daily. The animal room was illuminated from 8:00 a.m. to 9:00 p.m. and the room temperature was controlled at approximately 26°C. Two weeks before, during, and 2 weeks after the repeated MA administration period described below, ad lib water and food were available in the cage.

The four experimental monkeys were killed at least 1 month after the behavioral experiment was completed for the neurochemical assays described below. During this one month period the animals were maintained under ad lib water and food conditions. Two male and one female rhesus monkeys that had histories of receiving single doses of psychoactive drugs but no repeated MA regimen were also killed as non-treated controls for neurochemical assays. These three control monkeys were maintained with ad lib water and food under the same housing conditions as the experimental animals.

Apparatus

The experimental chamber consisted of 2 wooden sound-attenuating cubicles placed side by side with a 45×50 cm opening in the common wall. One cubicle (91×77×76 cm) contained a conical knob connected to a force transducer (termed "force lever") at the far end of a plastic tube connected to the common wall of the 2 cubicles. The second cubicle (76×76×91 cm) contained a metal monkey cage with one wall removed to allow the monkey access to a plastic panel built into the opening in the common wall between the two cubicles. On the left side of the plastic panel were 4 stimulus lights, arranged vertically. A cup into which water was delivered was located to the right of the bottom stimulus light. This cup was connected by silicone tubing to a peristaltic infusion pump (Cole-Parmer Instrument Co., No. 7540X, Chicago, IL). Operation of this pump resulted in the delivery of water into the cup from a reservoir. The plastic tube (7 cm in diameter) which projected into the other chamber was attached to the plastic panel to the right of the cup. The length of the tube from the opening to the force lever could be adjusted from 21 to 33 cm. When the tube was fully extended, it was necessary for the monkeys to completely extend their arm and digits in order to press the force lever. Variations in the force exerted on the lever were monitored by a system composed of a force transducer (Statham Instruments, Inc., No. UC3, Oxnard, CA), a Beckman Dynograph (Beckman Instruments, Inc., No. R411, Arlington Heights, IL), and solid-state programming and recording equipment (BRS/LVE, Beltsville, MD). Periodically, the system was calibrated by suspending weights from the lever.

Procedure

Behavioral baseline. Sessions were signalled by the illumination of the top stimulus light on the plastic panel. In order to receive a reinforcer, the monkey was required to place one arm into the plastic tube which was extended to its full length of 33 cm and press the lever with a force between 25 and 40 g for 5 sec. If the force exerted was outside these limits (less than 25 g or more than 40 g) for more than 30 msec, the time requirement reset. If the time requirement was completed, the pump was activated for approximately 7 sec to deliver 1.5 ml of water. During water delivery, all lights were extinguished in the cubicle and lever-pressing had no programmed consequences. A session was terminated after 50 reinforcers were delivered or 30 min had elapsed, whichever came first. Sessions were conducted five days a week, Monday through Friday.

Feedback for performance was provided using the bottom 3 stimulus lights on the panel. The bottom light was illuminated when the exerted force was above 40 g. The next light was illuminated when lever-pressing was within the specified limits, i.e., when a force of between 25 and 40 g was exerted. The next light was illuminated when the exerted force was between 10 and 25 g; below 10 g, only the top session light was illuminated.

Four elapsed timers were used to record the monkey's performance. One timer recorded total session time, excluding the time water was delivered. In addition, the total time a monkey responded with a force between 10 and 25 g (below-band responding), the total time a monkey responded within the specified limits (in-band responding) and the total time a monkey responded with a force greater than these limits (above-band responding) were recorded separately on the other 3 timers. Two counters recorded the number of times the response force entered the required band width (from either below or above band) and the number of water deliveries obtained within the 30-min time limit.

TABLE 1

MEASURES OF FORCE LEVER PERFORMANCE

In-Band Efficiency*	=	$\frac{\text{No. of Reinforcers Delivered} \times 5 \text{ (sec)}}{\text{In-Band Responding Time (sec)}}$
Entrance Score†	=	$\frac{\text{Total Band Entrances}}{\text{No. of Reinforcers Delivered}}$
Work Rate	=	$\frac{\text{Total Responding Time (sec)}}{\text{Session Time (sec)}}$

*If responding is completely eliminated, this measure cannot be calculated. If in-band responding time is less than 5 sec, the session is not included in analyses.

†If the number of reinforcers is 0, this measure cannot be calculated.

Initial dose-effect determinations. When responding on the force lever showed no consistent trends over several sessions, dose-effect functions for MA, APO, and HAL were determined. The function for MA was determined last in each monkey; the HAL function was determined first in 2 monkeys (9072 and 9073) and APO was first for the other two monkeys (9069 and 9077). Doses of each drug were given in ascending order. All injections were given intramuscularly, 5 min before the session for APO, and 20 min before the session for MA and HAL. Saline was given as a vehicle control once during each dose-effect determination. Injections were given no more than twice a week. Saline or drugs were tested only when responding during the training session just prior to the test session was similar to previous pre-test sessions. Performance during these pre-test training sessions was used as the baseline for comparison.

Repeated MA administration. Daily sessions were terminated following the completion of the dose-effect determinations for the 3 drugs, and food and water became available ad lib. Two weeks later, a 14 day regimen of repeated MA administration began. Drug was administered subcutaneously 4 times per day (6:00 a.m., noon, 6:00 p.m. and midnight). Total daily dose increased over the 14 days as follows: 4, 4, 8, 8, 16, 16, 24, 24, 28, 32, 32, 36, 40 and 40 mg/kg/day. Grossly observable behavior of the monkeys was noted before and after each injection and body weights were measured every 3 or 4 days during the 14 day period.

Dose-effect redeterminations. Two weeks following the last day of the repeated MA regimen, daily sessions were begun and food and water intake were limited in the same manner as described for the initial dose-effect determinations. Beginning one month after the last day of repeated MA administrations, dose-effect functions for the three drugs were redetermined in the same manner as before except that the order was MA, HAL and APO for monkeys 9069 and 9077, and MA, APO and HAL for monkeys 9072 and 9073.

Data Analyses

The measures shown in Table 1 were used in the data analyses. These measures have previously been used by other investigators employing this procedure [3, 11, 19, 21]. In-band efficiency can vary between 0 and 1.0 with higher values indicating well-controlled responding on the force lever. This measure is independent of the number of reinforcers earned. Entrance score is the average number of band entrances made per reinforcer delivered and can be increased by tremors or premature termination of responding. The minimum score is 1.0. Work rate also varies between 0 and 1.0 and measures the proportion of the session the animal spends pressing the lever with 10 or more grams of force. Changes in work rate are considered indicative of nonspecific treatment effects.

Neurochemical Assays

All monkeys were anesthetized with sodium pentobarbital at 25 mg/kg, IP and killed by exsanguination from the jugular artery 6–10 months after the last day of the repeated MA regimen. The monkey brains were dissected to yield both left and right samples of frontal cortex, caudate nucleus, thalamus, hypothalamus, midbrain and brain stem. These brain samples were stored in liquid nitrogen until assayed. Concentrations of dopamine (DA), norepinephrine (NE) (only for hypothalamus), and serotonin (5-HT) were determined by high performance liquid chromatography coupled with an electrochemical detector.

Drugs

Methamphetamine (*d*-methylamphetamine) hydrochloride was supplied by the National Institute on Drug Abuse and apomorphine hydrochloride (Merck and Co., Inc., Rahway, NJ) and haloperidol lactate (Haldol injection, McNeil Laboratories, Fort Washington, PA) were obtained commercially. MA and APO were dissolved and HAL was diluted in physiological saline in a concentration such that injection volumes were 0.1 ml/kg. The doses tested for MA, APO and HAL ranged from 0.13 to 5.7 mg/kg, from 0.031 to 0.5 mg/kg, and from 0.008 to 0.063 mg/kg, respectively. In the repeated MA regimen, methamphetamine hydrochloride was dissolved in physiological saline in concentrations of 25 mg/ml for the 1–4 mg/kg/inj doses and 50 mg/ml for the 5–10 mg/kg/inj doses. All drug doses were calculated on the basis of their salts.

RESULTS

Initial dose-effect determinations. After several months of training, all four monkeys learned to press the lever with a force between 25 and 40 g for 5 sec and obtained 50 water reinforcers in approximately 10 min. Responding during training sessions was stable throughout the initial dose-effect determinations. Control values were obtained by averaging across all sessions occurring on the day before each test session (see open circles at C in Figs. 2–4). In-band efficiency was 0.87 and above, entrance score was 2.91 and below, and work rate was 0.34 and above across monkeys. The pattern of responding and these measures were unaffected by saline injections (see the top record in Fig. 1 and open circles at S in Figs. 2–4).

At the higher doses, MA decreased in-band efficiency and increased the entrance score in all monkeys except 9072. The lowest doses which decreased in-band efficiency ranged from 0.25 to 1 mg/kg (Fig. 2). At the same doses, entrance score was increased and in monkey 9073, this score was markedly increased at 2 mg/kg. There were differences across monkeys in terms of their sensitivity to the rate-decreasing effects of MA. Decreases in work rate to below 10% were produced by doses ranging from 0.25 to 2.8 mg/kg. For monkeys 9073 and 9077, the dose of 1.0 mg/kg which altered the efficiency and entrance score had little effect on work rate. For monkey 9069, the dose which altered the in-band efficiency almost totally eliminated responding. Although in-

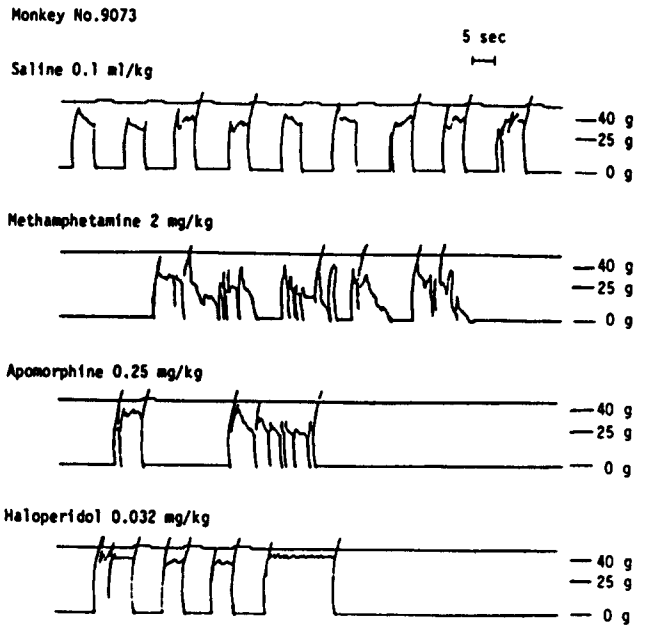

FIG. 1. Sample analog recordings of force lever performance of monkey 9073 after intramuscular administration of saline or drugs. The tracing moves horizontally with time and vertically with changes in the force exerted on the lever. Pressing on the lever with a force of between 25 and 40 g for 5 sec was reinforced with water. The notches in the line at the top of each recording indicate delivery of water.

band efficiency could be calculated at this dose because response time did exceed 5 sec, the entrance score could not be calculated because the number of reinforcers delivered was zero. For monkey 9072 even the dose (1.0 mg/kg) which markedly affected work rate resulting in the delivery of 4 reinforcers had no effect on the other measures of performance. A sample analog record of responding after MA is shown in Fig. 1 for monkey 9073. A response pattern of frequent band entrances and the inability to complete the time requirement can be seen.

For three of the monkeys, the dose-related decrease in work rate produced by APO was more gradual than in the case of MA. At the same doses which affected work rate, in-band efficiency was not decreased to the same extent (Fig. 3). In contrast, monkey 9077 showed a marked decrease in in-band efficiency at the dose of 0.13 mg/kg but work rate was unaffected. Entrance score was increased markedly at higher doses in 2 monkeys (9069 and 9077). A sample analog record for this drug (Fig. 1, third record) indicates a response pattern with frequent band entrances and long pauses.

With HAL (Fig. 4), in-band efficiency was decreased and entrance score was increased in all monkeys except one (9069). For this monkey, these measures could not be calculated at the highest dose because the in-band responding time was less than 5 sec and no reinforcers were delivered. Work rate decreased in a dose-dependent manner in all monkeys. Decreases in in-band efficiency and increased entrance scores were found only at the highest dose which markedly decreased work rate. A sample analog record for HAL indicates a response pattern with a long duration of lever pressing above band and long periods of pausing for monkey 9073

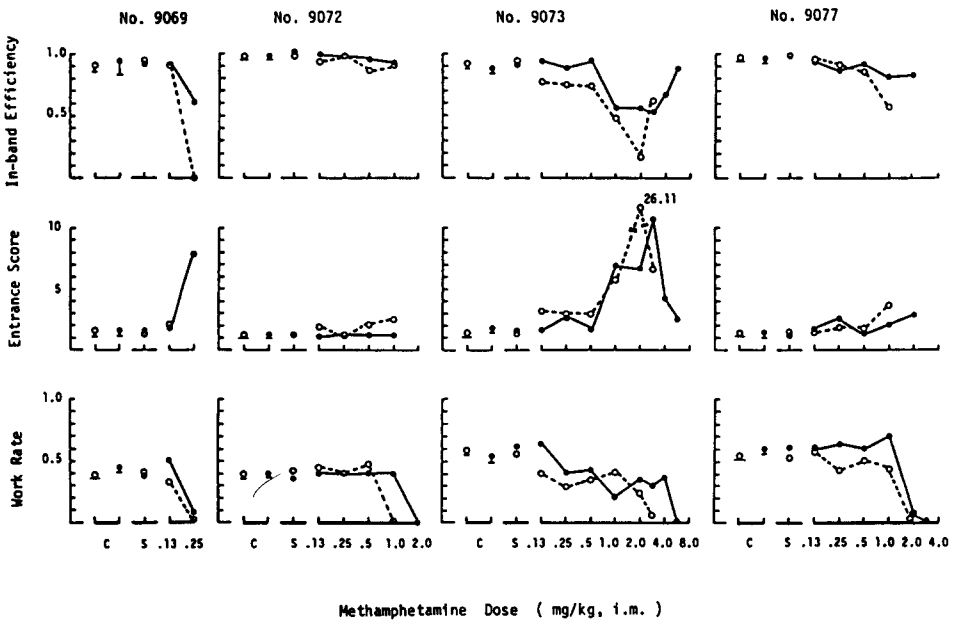

FIG. 2. Effects of methamphetamine on force lever performance in 4 rhesus monkeys before (open circles) and after (solid circles) repeated methamphetamine administration. See Table 1 for the explanation of the vertical axes. The horizontal axes indicate doses on a log scale. The data points above C indicate averaged values with standard deviations across all sessions occurring on the day before each test session. The data points above S indicate values in the saline test sessions.

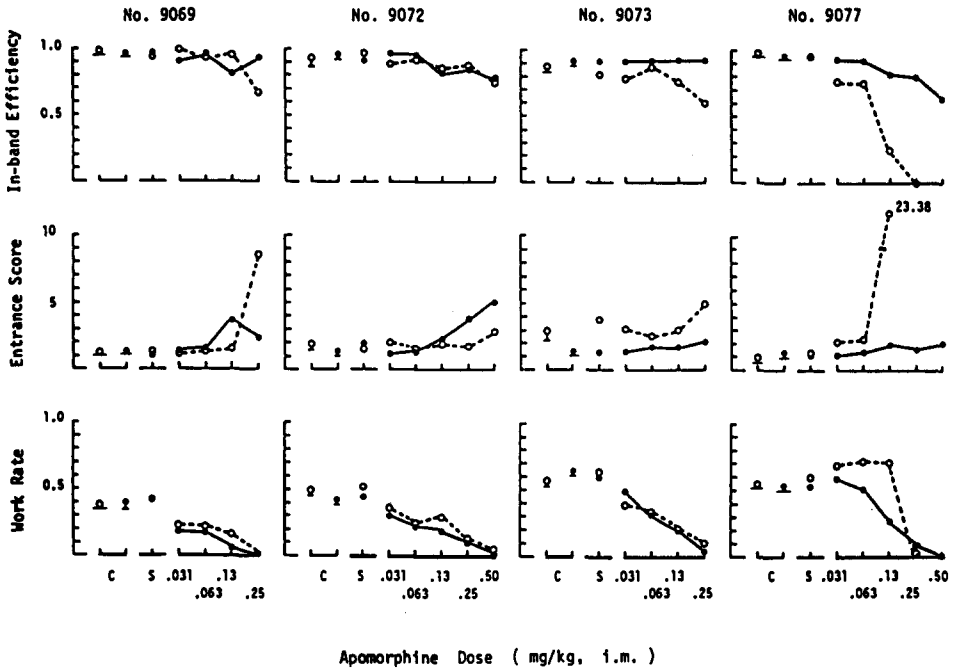

FIG. 3. Effects of apomorphine on force lever performance in 4 rhesus monkeys before (open circles) and after (solid circles) repeated methamphetamine administration. Other details as in Fig. 2.

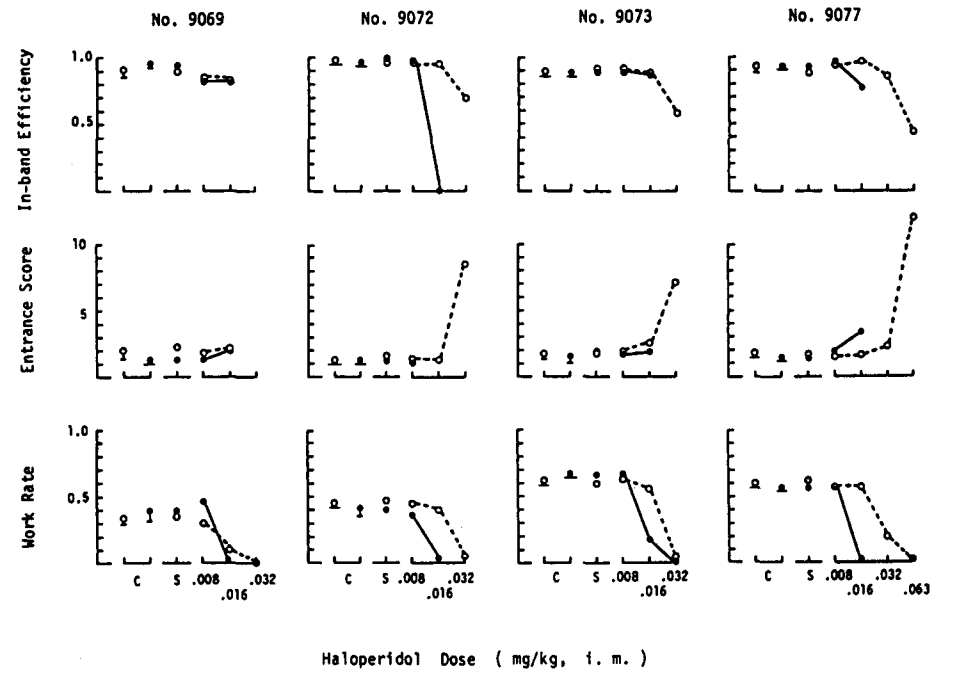

FIG. 4. Effects of haloperidol on force lever performance in 4 rhesus monkeys before (open circles) and after (solid circles) repeated methamphetamine administration. Other details as in Fig. 2.

(Fig. 1, bottom record). However, this analog record does not completely reflect the changes in the measures in Fig. 4 because the record presented is only for a limited period of the total session.

Using decreases in work rate as a criterion, the sensitivity of each monkey differed across drugs. For MA, the order from the most sensitive to least was 9069, 9072, 9077 and 9073 (Fig. 2). The order was 9069, 9073 or 9077 and 9072 for APO (Fig. 3), and 9069, 9072 or 9073 and 9077 for HAL (Fig. 4).

Repeated MA administration. During the first 7 days of the repeated MA administrations, all monkeys showed a decrease in food intake and typical behavioral changes

produced by amphetamine-like drugs such as restlessness, stereotypy, increased locomotion and hypervigilance. However, on days 8 and 9, food intake increased and monkeys exhibited signs of ataxia. Between days 10 and 14, activity levels decreased and monkeys were tremulous; monkey 9072 remained in a prone position on the floor of the cage. By day 14, body weights had decreased to an average of 84.2%. Although the monkeys were restless and slept during the daytime, 2–4 days after the repeated MA administration regimen was terminated, their gross behavior returned to normal. Eleven days after the repeated MA administrations were terminated, body weights had recovered to 95% of pre-regimen.

Dose-effect redeterminations. When the daily experimental sessions were re-initiated, responding returned to baseline levels during the first session. Responding was stable throughout the dose-effect redeterminations and the average values of the three measures across all pre-test control sessions were almost identical to those during the initial dose-effect determinations (see solid circles at C in Figs. 2–4). Responding was unaffected by saline injections as before (see solid circles at S in Figs. 2–4).

With MA, in-band efficiency and work rate were less affected during the dose-effect redeterminations compared to those measures during the initial dose-effect determinations, although the differences were not marked in some monkeys (Fig. 2). In-band efficiency was relatively high even at the doses where work rate was decreased markedly. Changes in entrance score were similar for both determinations.

With APO, in-band efficiency and entrance score were less affected during the dose-effect redeterminations compared to those measures during the initial dose-effect determinations with the exception of monkey 9072 which showed similar changes in in-band efficiency but more increases in entrance score. In contrast, changes in work rate were similar to the initial dose-response determination so that when in-band efficiency was relatively high, work rate was decreased markedly.

With HAL, in-band efficiency for 2 monkeys (9072 and 9077) and work rate for all monkeys were more affected during the dose-effect redeterminations than during the initial dose-effect determinations. In-band efficiency as well as entrance score was unchanged in monkeys 9069 and 9073.

Neurochemical assays. The monkeys which received repeated injections of MA showed a 32% decrease in DA levels in the caudate nucleus compared to controls (8.6 ± 1.4 vs. 12.6 ± 1.5 μg/g of tissue) as well as a 71% decrease in 5-HT levels in the frontal cortex (0.02 ± 0.01 vs. 0.07 ± 0.01 μg/g of tissue). There were no significant changes in levels of DA or 5-HT levels in any of the other brain regions assayed. There was also no difference in NE levels in the hypothalamus.

DISCUSSION

The dose-effect relationships for MA, APO, and HAL before the period of repeated MA administrations showed that all 3 drugs disrupted responding on the force lever. All 3 drugs decreased work rate, in-band efficiency, and increased entrance score in a majority of monkeys. The decreases in in-band efficiency indicate a general deterioration in performance while increases in the entrance score indicate tremor or some other dysfunction such as muscle rigidity. Although there were differences between drugs, they were subtle and it appears that no single type of dysfunction can be identified for each drug. The results with MA are qualitatively similar to those reported by Johanson *et al.* [11] and Falk and his colleagues [3,21]. That is, at doses which did not decrease work rate, there was an increase in phasic activity or tremors. Similarly, the increase in the total number of entrances into the band observed with HAL corresponds with that observed with chlorpromazine in rats [3]. However, since increased tremors have been observed with both DA agonists and antagonists, it is unlikely due to a specific biochemical mechanism.

During the repeated MA administration, anorexia, stereotypy and increased locomotor activity were initially seen but these effects diminished as the administration period continued. Although the monkeys were extremely debilitated by the drug administrations during the entire 2-week period, they rapidly recovered when drug administration was terminated.

Fine motor control behavior by the rhesus monkeys was well controlled even after the period of repeated MA as well as the 40 day interruption in training sessions. It has been reported that the basal ganglia play an important role in motor function and that neurochemical changes in this region produce motor dysfunctions, such as Parkinson's disease [9]. Although there were decreases observed in caudate nucleus dopamine levels in the treated monkeys compared to the non-treated controls, the treated monkeys showed neither gross behavioral changes nor dysfunctions of the fine motor control performance after repeated MA administration. However, the changes in monoamine levels produced by repeated MA administration may not have been severe enough to cause observable behavioral changes.

Although the neurochemical changes did not cause observable behavioral changes, sensitivity changes were detected when drugs were administered. A comparison of the dose-effect functions obtained before and after the period of repeated MA administration shows some tolerance to MA in contrast to supersensitivity to HAL. These findings are in accord with previous research. For instance, Finnegan *et al.* [4] reported tolerance to the effects of MA and APO and supersensitivity to HAL on responding maintained under a differential-reinforcement-of-low rate (DRL) schedule in rhesus monkeys following a period of repeated administration of MA. However, the degree and consistency of tolerance to MA and APO was greater in the study by Finnegan *et al.* [4] than in the present study. This might be attributable to the different behaviors being studied or to the fact that the caudate nucleus DA depletions were greater in the study by Finnegan *et al.* [4]. A study by Lucot *et al.* [16] using measures of general activity has as well reported differences in sensitivity to APO, MA and HAL in rats whose caudate nucleus DA levels had been depleted by repeated administration of MA.

Taken as a whole, all these studies suggest that the changes in sensitivity to APO, MA and HAL are a result of the depletion of DA produced by the repeated administration of MA. As previously demonstrated, these depletions do not alter the sensitivity of post-synaptic dopamine receptors [4, 25, 26]. Tolerance to MA can be understood as a consequence of the lower levels of DA available for release from the terminals in the caudate nucleus. The super-sensitivity to HAL may be attributed to the fact that the depletion of DA in nerve terminals would lead to a decrease in the amount of DA released by normal neural processes. HAL would therefore be competing with a lower concentration of dopamine for post-synaptic receptor sites. As argued elsewhere [4], tolerance to APO may be attributable to the fact that as a

directly acting dopamine agonist, apomorphine's effects are additive with the effects of dopamine released by the ongoing level of impulse flow in the nigrostriatal system. If the quantity of dopamine released by functional transmission is lower, then a higher dose of APO would be necessary to produce comparable stimulation of dopamine receptors.

In addition to dopamine depletions, the repeated administration of MA produced a significant decrease in 5-HT in the frontal cortex. Although not statistically significant in these animals there were also decreases in 5-HT levels in the hippocampus. In previous studies depletions were also seen in the hippocampus (Preston, Personal Communication). It remains for future research to determine whether these depletions cause changes in the sensitivity of monkeys to the behavioral effects of 5-HT agonists and antagonists. Such results would give further support to the idea that drug challenges can be used to reveal changes in brain neurochemistry not observable in normal behavior.

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