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Effects of Dopaminergic Agents on Eye Tracking Before and After Repeated Methamphetamine[1]

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ANDO, K , C E JOHANSON AND C R SCHUSTER *Effects of dopaminergic agents on eye tracking before and after repeated methamphetamine* PHARMACOL BIOCHEM BEHAV **24**(3) 693–699, 1986 —The effects of methamphetamine (MA), apomorphine (AP) and haloperidol (HAL) on eye tracking function were tested in rhesus monkeys Three rhesus monkeys were trained to track with their eyes a disk-shaped projected image that oscillated along a horizontal plane on a screen, using a training procedure in which responses on a lever were reinforced with water only when the center of the disk dimmed for a brief period Eye movements were recorded by electrooculography (EOG) The effects of intramusuclar administration of MA, APO and HAL on responding were compared before and after a 8–14 day period of repeated MA administration During this regimen, MA was given in 4 divided doses starting at a total daily dose of 4 mg/kg/day and increasing to 16–40 mg/kg/day All three drugs disrupted performance during both the initial dose-response determination as well as during the redetermination following the regimen However, tolerance to MA in 3 monkeys and to APO in 2 monkeys was observed after the regimen, while no marked sensitivity change was observed to haloperidol Since other data reported elsewhere have shown that dopamine is depleted in the caudate after similar repeated administration regimens, long lasting brain dopaminergic changes are likely present in these monkeys Therefore, these results suggest that the changes in sensitivity to the drugs that were observed in terms of eye tracking function are related to dopamine depletion in the brain

Methamphetamine Apomorphine Haloperidol Eye tracking Smooth pursuit eye movements Rhesus monkeys

EYE tracking is an integrated function consisting of specific eye movements as well as behavioral processes If a target in front of the eyes of a normal human subject is oscillated sinusoidally along a horizontal plane (simple harmonic motion), the subject can emit smooth pursuit eye movements in which the velocity of the movement corresponds to that of the target However, in certain pathological conditions of the CNS, smooth pursuit eye movements are impaired [19] Disruption of smooth pursuit eye movements has also been reported for schizophrenic patients [6, 8, 13] In addition, drugs produce specific effects on pursuit eye movements in normal human subjects [7, 11, 15, 17] In a recent study, rhesus monkeys were trained to track a disk-shaped image oscillating horizontally in simple harmonic motion by reinforcing responses on a lever with water only when this response coincided with a brief period signalled by the dimming of the central part of the disk [1] After training, the effects of phencyclidine, secobarbital and diazepam on eye tracking function, which encompasses both smooth pursuit eye movements and the lever pressing behavior, were evaluated Based on the similarities between these drug effects on smooth pursuit eye movements in rhesus monkeys and the available human data, the potential usefulness of this animal model in predicting drug effects on oculomotor function in humans was suggested Since such functions as integration of incoming sensory stimuli and fine motor movements (e g , eye tracking) are thought to be related to the extrapyramidal system of the basal ganglia of the brain, further studies of this kind might be helpful in clarifying the relationship between eye tracking function and dopamine in the brain In previous studies, it has been reported that repeated methamphetamine (MA) administration at high doses produces long-lasting changes in the catecholaminergic system in the brain, including dopamine terminal degeneration of dopamine nerve endings, and dopamine depletion in the striatum [18, 20, 21] These changes were correlated with

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sensitivity changes to dopaminergic agents observed in schedule-controlled behavior in rhesus monkeys, including tolerance to MA and apomorphine (APO) and supersensitivity to haloperidol [3] Similar results were also found with methamphetamine and haloperidol when the behavior involved performance requiring fine motor control [2]

The purpose of the present experiment was to extend these findings by determining the effects of MA, APO and HAL on eye tracking function in rhesus monkeys and also to study the changes in sensitivity to these drugs after long-lasting changes have been produced in the dopaminergic system of the brain by repeated MA administration

METHOD

Animals

The animals used were three adult male rhesus monkeys weighing between 6 9 and 9 0 kg at the start of the experiment These monkeys had been used previously in the eye tracking experiment testing the effects of single doses of phencyclidine, secobarbital and diazepam [1] but they had no history of repeated administration of psychoactive drugs Each monkey was housed individually in a metal home cage (62×70×60 cm) located in an animal room that also housed 10 to 15 other monkeys, and was fed 100 g of monkey chow (No 5038, Ralston Purina, St Louis, MO) daily at least 1 hr prior to the experimental session Daily water intake was limited to 150–200 ml, including water deliveries during the experimental sessions Sugar cubes saturated with liquid vitamins were also given after experimental sessions The experimental sessions were conducted every day except Saturdays, Sundays and holidays On the days when experimental sessions were not conducted, each monkey was given access to 200 ml of water in his home cage as well as 100 g of chow On Friday, approximately 1000 ml of additional water was given to each monkey in his home cage after completion of the experimental session The animal room was illuminated from 8 a m to 9 p m and the room temperature was controlled at approximately 26°C

Apparatus

The experiment was conducted with each monkey seated in a plastic restraining chair (Plas-Labs, Lansing, MI) placed inside a wooden enclosure (80 cm wide × 86 cm long × 182 cm high) A panel with a response lever (No PRL-001, BRS/LVE, Beltsville, MD) that could be activated by a force of approximately 100 g was mounted on the front of the chair Head movement was limited by plastic panels at each side and on top of the monkey's head Water was delivered using a metal nozzle placed into the monkey's mouth

A white screen (28×59 cm) was mounted directly in front of the monkey inside the wooden enclosure The center of this screen was located at eye level 79 cm from the point halfway between the monkey's eyes An image appearing as a red disk was projected onto the screen by light emitting diodes (LED) through an optical path system located above and behind the monkey This disk consisted of an outer annulus (diameter 2 5 cm) and an inner disk (diameter 1 0 cm) which were projected by separate LEDs The outer annulus was formed by reflecting the light of one LED off a mirror with a small opening in the center, and the inner disk was projected by a second LED directly through this small opening The image on the screen appeared as one homogenous disk when the current supply to the 2 LEDs was properly set When the current to the second LED was decreased, the inner disk appeared dimmed Although the luminances of the outer annulus and inner disk were not calibrated, the operating currents of the two LEDs and their differences were constantly regulated throughout the experiment

During the experimental sessions, the composite disk image was made to oscillate sinusoidally in the horizontal plane (simple harmonic motion) through 30 degrees of visual angle (42 3 cm on the screen) at a frequency of 0 8 Hz by reflecting the image off a mirror affixed to a galvanometer (Gulton Industries, East Greenwich, RI) that was activated by an amplified voltage signal from a signal generator (No 7060, Exact Electronics, Tallamook, OR)

Electrooculographic (EOG) recordings were obtained using silver-silver chloride skin electrodes (No 650437, Beckman Instruments Arlington Heights, IL) placed at the outer canthus of each eye and at the center of the forehead of each monkey The amplified EOGs were recorded on a frequency modulation cassette recorder (No FRC-1402D, Sony, Tokyo, Japan) and simultaneously displayed on chart paper by a dynograph (No R411, Beckman Instruments, Arlington Heights, IL)

Experimental contingencies were arranged and lever pressing was recorded by solid-state programming and recording equipment (BRS/LVE, Beltsville, MD) located in an adjacent room

Procedure

For two of the monkeys (5105 and 6048), the enclosure was totally darkened during the experimental sessions For the third monkey (5101), a 15 W lamp mounted on the ceiling of the enclosure was illuminated, since this monkey did not respond consistently when the enclosure was totally darkened Trials were signalled by a pure tone generated by a Sonalert (No 112-01, BRS/LVE, Beltsville, MD) A single response on the lever (observing response) terminated the tone and the oscillating disk was projected on the screen The inner disk was dimmed for 0 5 sec under a random time schedule with an average interval value of 10 sec Pressing the lever during this 0 5 sec period or within 0 1 sec resulted in the delivery of 1 5 ml of water A trial was terminated either with the delivery of water or if the monkey pressed the lever at any other time during the trial (incorrect response) Upon termination of a trial, there was a 3 5 sec time-out followed by presentation of the pure tone beginning the next trial If no response occurred after the observing response, the disk was continuously presented and the inner disk was dimmed under the random time schedule During these training sessions no electrodes were attached to the monkey and the session was terminated after 99 reinforcers had been delivered

Dose-Effect Determinations Before Repeated MA Administration

When the percent of correct responses ((correct responses/disk dimmings)×100) was above 95% during training sessions, drug and saline tests were begun In test sessions, the effects of MA, APO, and HAL on eye tracking function were determined using a cumulative dose procedure in which the dose-effect function for each drug was determined in blocks of test trials with different doses of the same drug being tested on the same day [22] Each block of trials was identical and consisted of (1) a 7 min lever press recording

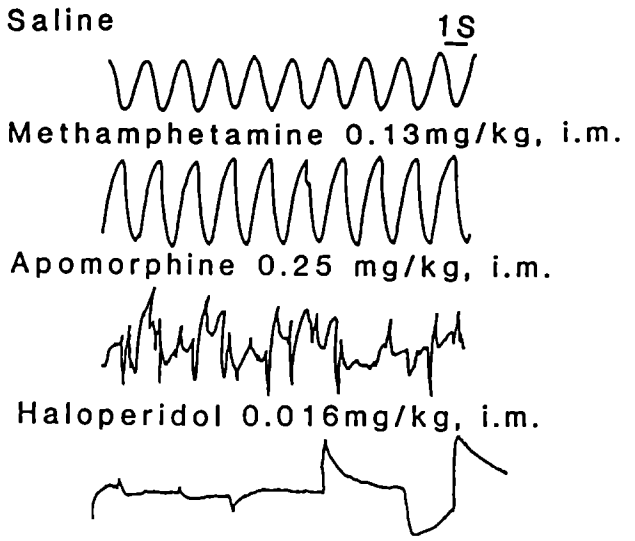

FIG 1 Drug effects on pursuit eye movements in monkey 6048 shown in an electrooculogram (EOG) recording Doses are expressed as cumulative doses A disk projection on the screen in front of the monkey's eyes was oscillated sinusoidally in the horizontal plane at a frequency of 0 8 Hz (see text)

component during which eye tracking trials were conducted as previously described, and (2) a 4 min EOG recording component The EOG recording component itself was comprised of 5 segments During each of these segments, the schedule contingencies were discontinued and the inner disk was not dimmed However, the entire disk was presented continuously, but lever pressing (incorrect responses) had no programmed consequence (i e , did not result in a time-out) After 40 sec had passed, the schedule contingencies were reinstated with the inner disk dimmed under the same random schedule, and each segment was terminated after a correct response (reinforced response), an incorrect response, or 15 sec, whichever came first The next EOG recording segment began immediately

At the start of a test session, physiological saline (0 05 ml/kg) was injected intramuscularly into the vastus lateralis muscle of the monkey, and the first block of test trials began 5 min later After its completion drug was administered at a certain dose (X mg/kg) by the same route and in the same volume as saline Five min later the second block began Additional test blocks (up to a total of six) were given by injecting the drug at X mg/kg (third block cumulative dose, 2X mg/kg), 2X mg/kg (fourth block cumulative dose, 4X mg/kg), 4X mg/kg (fifth block cumulative dose, 8X mg/kg) and 8X mg/kg (sixth block cumulative dose, 16X mg/kg), respectively, in the same manner as in the earlier blocks The interval between successive injections was 18 min The decision to conduct additional blocks of test trials was based upon the effects of the drug If a drug at a certain cumulative dose produced a marked decrease in the percent of correct responses during a block of test trials, no further testing was done and the test session was terminated During control sessions, saline injections were given prior to each of the six blocks Drug or saline test sessions were generally given once a week for each monkey and saline and each drug were tested twice EOG recordings were not always repeated even though the electrodes were attached to the monkey and the EOG recording components were unchanged. Between test sessions, the training sessions described earlier were given every day except Saturdays, Sundays and holidays

After completion of each test session, the monkey was removed from the wooden enclosure to the illuminated experimental room while still remaining in the chair and eyeblink frequency was measured for 3 min to determine whether the changes in EOG pattern might be due to changes in blink frequency

Repeated MA Administration

After obtaining duplicate dose-effect determinations for the 3 drugs and saline, the daily sessions were terminated and food and water became available ad lib After 2 weeks without testing, a repeated MA administration regimen began MA was administered subcutaneously 4 times per day (6 a m , noon, 6 p m and midnight), and the total daily doses were as follows 4, 4, 8, 8, 12, 12, 16, 20, 24, 28, 32, 36, 40, and 40 mg/kg/day (14 days) in monkey 5101, 4, 4, 8, 8, 8, 12, 16, 20, and 24 mg/kg/day (10 days) in monkey 5105, and 4, 4, 8, 8, 12, 12, 16, and 12 mg/kg/day (8 days) in monkey 6048 The dose of each injection was always 1/4 of the total dose for that day except on the last day in monkey 6048 in which the fourth injection (4 mg/kg) was not given The regimen for each monkey was intended to last for 14 days, but it was not possible to continue MA administration up to 14 days in 2 of the monkeys (5105 and 6048) because of a deterioration in their physical condition The monkeys' gross behavior was observed both before and after each injection, and body weights were measured 1 day before the regimen, 7 days after the start of the regimen, and after its completion

Dose-Effect Determination After Repeated MA Administration

Sixteen to twenty-two days after the final day of repeated MA administration, daily water intake was limited to 150–200 ml and training sessions were reinitiated as before Beginning one month after the last day of the repeated MA administration, the dose-effect functions for the 3 drugs and saline were redetermined during test sessions in the same manner as previously described

Data Analysis

The number of completed trials, observing responses, correct responses and incorrect responses in each test block were recorded as well as number of times that the inner disk was dimmed The percent of correct responses was computed as the ratio of total number of correct responses (reinforced responses) to total number of inner disk dimmings Cumulative latency, the duration from the onset of dimming of the inner disk to a correct response cumulated over the test block was also recorded If there was no response during the period when the inner disk dimmed 0 5 sec or for the 0 1 sec period immediately following, 0 6 sec was added to the cumulative latency The average response latency was defined as the cumulative latency divided by the total number of inner disk dimmings If there were no correct responses in a lever press component, the average response latency was the maximum value of 0 6 sec

The EOG records were visually inspected to count number of eye-tracking cycles during each 40 sec segment for each EOG recording component An eye-tracking cycle was defined as a sinusoid with a peak and trough correspond-

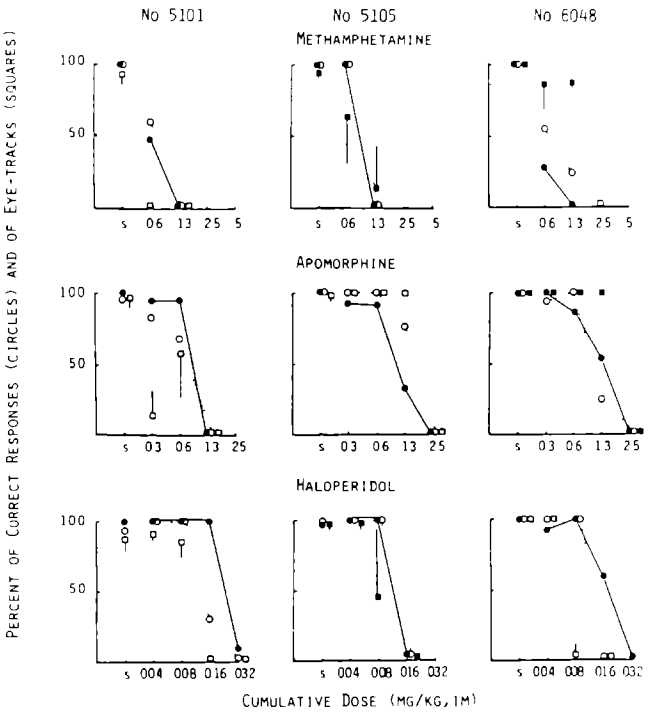

FIG 2 Effects of drugs on lever pressing behavior (percent of correct responses) and on pursuit eye movements (percent of eye tracks) in rhesus monkeys before the repeated methamphetamine administration Percent of eye tracks is indicated by mean and SD calculated from 5 segments of electrooculogram recording at each cumulative dose Test sessions with each drug were duplicated, although the pursuit eye movements were not always recorded twice Solid symbols and open symbols indicate the results of the 1st and 2nd test block sessions, respectively Cumulative dose is expressed on a log scale S indicates the results from a saline test session

ing to the peak and trough of the stimulus signal cycle regardless of whether the eye position tracing was smooth The percent of eye-tracks was computed from the ratio of the number of eye-tracking cycles to the number of signal cycles Means and standard deviations of this percentage were calculated across the five 40 sec segments in each EOG recording component

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 In the dose-effect determinations, MA and APO were dissolved and HAL was diluted in physiological saline to whatever concentrations necessary to deliver the doses at a fixed injection volume of 0 05 ml/kg The starting doses were 0 06 mg/kg for MA, 0 03 mg/kg for APO, and 0 004 mg/kg for HAL The maximum cumulative doses tested ranged between 0 13–1 mg/kg for MA, 0 13–0 5 mg/kg for APO, and 0 016–0 032 mg/kg for HAL In the repeated MA administration regimen, methamphetamine hydrochloride was dissolved in physiological saline in a concentration 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

In the training sessions before the start of the dose-effect determinations, all monkeys responded appropriately under the terminal contingencies All 99 reinforcers were delivered and the training sessions were approximately 40 min in duration The mean percent correct responses ranged between 94 and 100 across monkeys From direct observation of the monkeys, it appeared that their eye movements were synchronized with movements of the disk that is, the monkey's eyes moved in a simple harmonic motion which was confirmed by the EOG tracing In the saline test sessions, the lever press behavior over all 6 blocks was stable and similar to performance during training sessions The mean percent correct responses (±one standard deviation) over the 6 blocks in the two saline test sessions were 93 3±7 1 and 99 2±2 0 in monkey 5101, 100±0 and 100±0 in monkey 5105, and 99 2±2 0 and 100±0 in monkey 6048 The number of incorrect responses per session and the average response latency ranged between 0 and 1, and 2 6 sec and 4 5 sec, respectively, over these same 6 blocks Smooth pursuit eye movements were observed in the EOG recording periods (Fig 1, top record) and the mean percent of eye tracks in the saline test sessions was 95 8±2 2 in monkey 5101, 99 9±0 3 in monkey 5105 and 99 0±1 4 in monkey 6048 The numbers of eye blinks per min after the completion of the saline test sessions were 11 5 in monkey 5101, 17 4 in monkey 5105 and 15 0 in monkey 6048

Dose-Effect Determinations Before Repeated MA Administration

As Fig 2 shows, MA decreased percent correct responses in a dose-related manner and responding was totally suppressed at 0 13 to 0 25 mg/kg The differences between the dose-response curves in each of the two duplicate test sessions across monkeys were minimal Percent eye tracks in monkey 5101 were almost zero at 0 06 mg/kg even though percent correct responses was only decreased by 50% In contrast, percent eye tracks decreased in a similar manner as percent correct responses in monkey 5105 Percent eye tracks did not decrease markedly in monkey 6048 even at doses where percent correct responses decreased markedly In all 3 monkeys, pursuit eye movements were smooth until they disappeared (Fig 1, 2nd record)

APO decreased percent correct responses in a dose-related manner and the two determinations were similar This measure decreased to zero at 0 13 and 0 25 mg/kg across monkeys The relationship between correct responses and percent eye tracks was similar to that found with MA, i e , percent eye tracks were more disrupted than correct responses in monkey 5101, less disrupted in 6048 and similarly disrupted in 5105 After APO at higher doses, the EOG recordings in all 3 monkeys showed jerky eye movements, indicating frequent eye blinks (Fig 1, 3rd record) HAL decreased the percent correct responses in a similar manner as the above 2 drugs The measure decreased to almost zero at 0 016 and 0 032 mg/kg Percent eye tracks decreased more markedly than the percent correct responses at the same doses in 3 monkeys EOG recordings after higher doses of HAL showed that the eyes usually fixated and sometimes moved saccadically (Fig 1, bottom record)

The number of incorrect responses per session did not

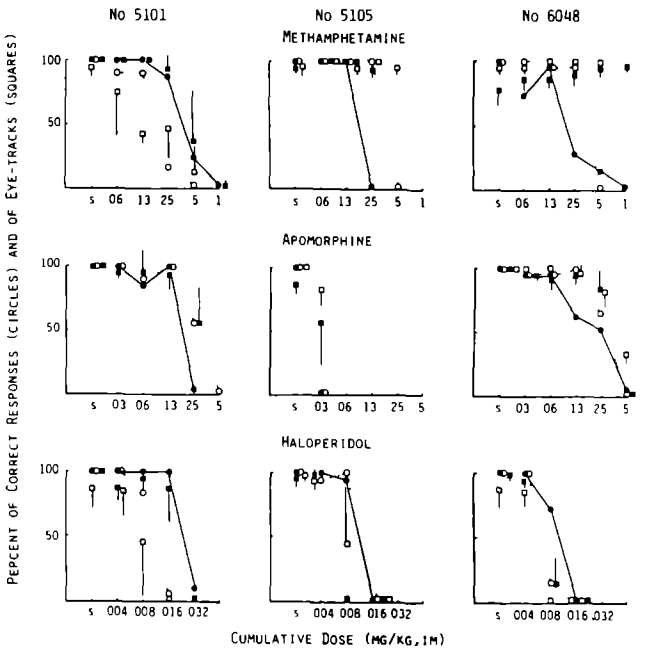

FIG 3 Effects of drugs on lever pressing behavior (percent of correct responses) and on pursuit eye movements (percent of eye tracks) in rhesus monkeys after the repeated methamphetamine administration Other details as in Fig 2

increase markedly after any of the 3 drugs except for an increase after HAL up to 13 at 0 016 mg/kg and up to 6 at 0 032 mg/kg in monkey 5105 and monkey 5101, respectively The average response latency increased in a dose-related manner with the 3 drugs The number of eye blinks did not change markedly with MA (8 3–27 2/m across monkeys), increased with APO (19–61/m across monkeys) and decreased with HAL (3 7–13 3/m across monkeys)

Repeated MA Administration

During the first 5 days of the repeated MA administration regimen, all 3 monkeys showed decreased food intake and behavioral changes typically produced by amphetamine-like drugs (e g , restlessness, stereotyped behavior, hypervigilance) In monkey 6048, the repeated MA administration was terminated after the third MA injection on day 8 because this monkey was found lying on the floor of the cage on day 5 and with eyes closed on days 7 and 8 Monkey 5105 continued to show typical behavioral changes on days 6 through 10, but the repeated MA administration was terminated after the fourth MA injection on day 10 because the monkey was found lying on the floor with closed eyes on the morning of day 11 Monkey 5101 continued to show typical behavioral changes and was able to complete the 14-day regimen By day 7 of the regimen, body weights across monkeys had decreased to 77–84% of pre-regimen weights After completion of the regimen, the monkeys were restless and slept during the daytime for 2–4 days and then their gross behavior returned to normal Body weights recovered to 84–97% of pre-regimen values across monkeys 2–3 weeks after termination of the repeated MA administration

Dose-Effect Determinations After Repeated MA Administration

When the training sessions were reinitiated, eye tracking behavior returned to baseline levels during the first session after 42–46 days of no daily sessions Percent correct responses in the first training session after the repeated MA administration ranged between 96–100% across monkeys In saline test sessions, stable eye tracking behavior and smooth pursuit eye movements were observed over the 6 blocks in all 3 monkeys Percent correct responses and the eye tracks were similar to pre-regimen values As Fig 3 shows, MA decreased percent correct responses in a dose-related manner There were only small differences between the two post-regimen dose-response determinations The dose-response function for MA after the repeated MA administration in each monkey was shifted to the right of the pre-regimen function 2–8-fold Percent eye tracks decreased with the decrease in percent correct responses in monkey 5101 but in the other 2 monkeys, percent eye tracks was unaffected at doses that decreased percent correct responses markedly For all monkeys higher doses of MA were required to affect percent eye tracks after the regimen compared to before

For apomorphine, the percent correct response functions were shifted to the right in 2 monkeys after the repeated MA administration but were shifted to the left in monkey 5101 Percent eye tracks also decreased in a similar manner but to a lesser extent than correct responses With haloperidol the dose-percent correct response functions were shifted to the left in monkey 6048 but did not change in the other 2 monkeys The dose-percent eye track functions for this drug after the repeated MA administration did not change in comparison with those before the repeated MA administration

With all 3 drugs, the changes in the number of incorrect responses and the average response latency were similar to those before the repeated MA administration except that the numbers of incorrect responses were 5 and 10 in both blocks with APO at 0 03 mg/kg in monkey 5105 From visual inspection of the EOG recording, the qualitative changes in smooth pursuit eye movements for each drug were similar to those before the repeated MA administration The number of eye blinks after each drug were similar to the changes observed before the repeated MA administration

DISCUSSION

In the present experiment, MA, APO, and HAL disrupted eye tracking function, as expressed by decreases in percent correct responses and percent eye tracks, in a dose-related manner The small discrepancies between duplicate tests for each drug indicated that the cumulative dose response procedure was reliable enough to allow observation of possible changes in sensitivity produced by repeated MA administrations MA, APO and HAL could be differentiated qualitatively in terms of their effects on smooth pursuit eye movements After MA smooth pursuit eye movements continued until a dose was reached that totally suppressed all eye tracking APO disrupted pursuit eye movements as a result of increased eye blinks The frequent eye blinks with APO have been reported for rhesus monkeys elsewhere, and the effect is suggested to be associated with brain dopaminergic hyperactivity [10] HAL, classified as a dopamine antagonist, decreased the number of eye blinks in the present experiment and disruptions in smooth pursuit eye move-

ments were characterized by eye fixation accompanied by some saccadic eye movements With APO and HAL, disruption of the pursuit eye movement was correlated with the disruption of lever pressing behavior On the other hand, with MA smooth pursuit eye movements were not disrupted in 1 monkey before, and in 2 monkeys after the repeated MA administration at doses which markedly disrupted lever pressing Based on these results, it may be suggested that the present experimental procedure for testing drug effects on eye tracking function is useful for differentiating the pharmacological effects of various psychoactive drugs

The repeated MA administration regimen produced typical amphetamine-like behavioral changes and decreases in body weight For 2 of the monkeys, the effects were debilitating and necessitated terminating the regimen after 8 and 10 days, respectively All the monkeys, however, appeared normal several days after the termination of the repeated MA administration Since previous studies have shown long-lasting neurochemical changes in brain dopaminergic systems for rats and rhesus monkeys after similar repeated MA regimens [2, 3, 20, 21], such changes were likely present in these monkeys But the neurochemical changes that may have occurred per se might not have been great enough to cause gross behavioral changes or disruptions of eye tracking function as observed in the patients of Parkinson's disease [9] However, tolerance was observed to MA in eye tracking function after the repeated MA administration which is in agreement with previous results from other studies in rats and rhesus monkeys [2, 4, 14, 16] For instance, Finnegan *et al* [3] reported the development of tolerance to MA after a regimen of repeated MA administration on responding maintained under a differential reinforcement of low rate schedule with rhesus monkeys In that same study there was a decrease in dopamine levels in the caudate and a decrease in 3H dopamine uptake by caudate tissue in the same monkeys in comparison with nontreated controls The authors speculated that the tolerance to MA could be understood as a consequence of the lower levels of dopamine available for release from the dopamine neuroterminals in the caudate nucleus Another study demonstrated that repeated MA administration caused neuroterminal degeneration of the striatum of rat brain [18] Although there is no direct evidence that eye tracking function in the present experiment is specifically attributable to the brain dopamine system in the basal ganglia, the approach used in the present study is a possible avenue to understanding the correlation between behavioral changes and neurochemical changes produced by drugs

Changes in sensitivity to APO were also observed, 2 monkeys showed tolerance and 1 monkey showed supersensitivity after the repeated MA administration The finding of supersensitivity was surprising since in the previous study by Finnegan *et al* [3] tolerance to APO was demonstrated in all 4 monkeys tested Furthermore, the one monkey showing the leftward shift received the greatest amount of MA The discrepancy might be attributable to the specific behavioral assay, to the fact that the actions of APO may be mediated in a complicated manner by interactions with both postsynaptic and presynaptic receptors, or to other, unknown factors

Although Finnegan *et al* [3] reported supersensitivity to the effect of HAL, this finding was not replicated in the present study The lack of sensitivity change to HAL might be attributable to the use of the cumulative dose response procedure but further research is required to demonstrate the relevant factors

In summary, the present results are similar to results obtained in previous studies comparing the behavioral effects of MA, APO and HAL before and after a regimen of repeated MA administration The present study however measured the effects of these drugs on a behavior presumably mediated by dopaminergic systems Nevertheless in the absence of drugs, the behavior remained unaffected perhaps because decreases in brain dopamine, not directly measured in this study, were too small However, the actions of MA and APO were changed by the repeated MA regimen in a manner parsimonious with the hypothesis that MA decreased brain dopamine particularly if considered along with the results of previous studies [2 3, 5, 16] It remains for future research to determine whether the sensitivity changes observed with the present drugs are also related to other neurochemical systems such as serotonin It may be suggested, however, that drug challenges can be used to reveal changes in brain neurochemistry not observable in normal behavior

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