Psychopharmacology (1983) 80:345–350

Psychopharmacology

L-Dopa and Piribedil Alter Different Components of Attentional Behavior Dependent on Dose

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Abstract. L-Dopa (3, 10, 30, 100 mg/kg) given SC after carbidopa, and piribedil (10, 30, 100, 300 mg/kg) had biphasic effects on investigation of a novel cup. Gerbils given a low dose of L-Dopa (10 mg/kg) or piribedil (10 or 30 mg/kg) investigated the cup more than did vehicle-injected gerbils, whereas those gerbils given a high dose of L-Dopa (100 mg/kg) or piribedil (300 mg/kg) investigated it less. L-Dopa, but not piribedil, also had biphasic effects on investigation of conspecific odors. The increase in duration with no increase in frequency of investigation suggested an inability to shift attention normally. High-dose attenuation of investigation is considered nonspecific, as many other drugs have the same effect. Locomotor activity scores showed no concomitant increase following low doses, but only a dose-dependent decrease. In addition, L-Dopa (100 mg/kg), but not piribedil at any dose tested, prevented the normal decrement in response to the cup 24 h after injection. As a high response is normally only shown when the stimulus is novel, the data suggest that L-Dopa at the high dose, but not piribedil, interfered with selective attention. Thus, the different dopamine agonists affected different aspects of attention. The data are discussed in relation to neural effects of the drugs as reported in the literature.

Key words: L-Dopa – Habituation – Gerbils – Piribedil (ET-495) – Attention – Behavior – Catecholamines – Investigation – Dopamine

Although attention is a ubiquitous part of all survival-related behavior, an operational definition first necessitates a separation from arousal and, second, a separation of distinct types or components (Spring et al. 1977; Spring 1980). Arousal is a state of consciousness, whereas attention can only be defined in relation to a particular external or internal stimulus. Additionally, attention is not a unitary process, but rather a composite of behaviors that can be defined separately and are mediated separately by the CNS. 'Awareness' of stimuli can be shown by overt investigation of a stimulus, or covertly with no outward sign. 'Maintenance' of attention must be defined for each species in relation to each stimulus. 'Selective attention' is necessary for memory to be stored, and is specific for each species and each stimulus. 'Shift' of attention is necessary when another appropriate stimulus appears.

In my laboratory, tests that use multiple measures of investigation of novel stimuli have been developed (Cheal 1978b; Cheal et al. 1982a) to provide quantitative data that differentiate between different types of attention. The tests utilize natural investigation of novel stimuli by the Mongolian gerbil, an active small rodent. Gerbils are used because they are more 'exploratory' (Thompson and Lippman 1972) and show less fear of novelty than rats (Osborne 1977; Miller and Holzman 1981). Normal gerbils reliably investigate novel stimuli and then lose interest in the stimulus. Several criteria of habituation (Thompson and Spencer 1966) have been demonstrated in these tests (Cheal 1978b; Cheal et al. 1982a). Memory of the stimulus has been shown up to 4 weeks after a 1-min exposure with no extrinsic reinforcers. Because of long-term memory, a drug injection can be given, followed by one 1-min trial and testing 24 h later to determine whether the gerbil remembers the stimulus seen during the period of acute drug effect. This methodology, called stimulus-elicited investigation, allows separation of attention from acute motor effects of the drug.

Loss of selective attention was inferred previously in experiments with apomorphine (APO)-treated gerbils, but not in experiments with amphetamine-treated gerbils (Cheal 1980). The APO pattern of responses was blocked by pimozide (Cheal 1980), a relatively selective dopamine (DA) receptor blocker (Andén et al. 1970; Denef et al. 1979), suggesting DA mediation of the effect. Amphetamine and APO could have different effects on selective attention because of the action of amphetamine on norepinephrine (NE) (Glowinski et al. 1966) or because of indirect effects of amphetamine compared to direct receptor action by APO (Andén et al. 1967). The importance of NE was supported by data in which APO failed to prevent habituation when gerbils were given a concurrent injection of the NE α-adrenergic receptor agonist, clonidine (Cheal 1982).

Because APO and amphetamine affected stimulus-elicited investigation differently, it was of interest to test other DA agonists, such as L-Dopa and piribedil (PIRIB). L-Dopa, the precursor of DA, induces large increases in brain DA without elevating NE turnover at doses up to 100 mg/kg (Andén et al. 1967; Everett and Borcherding 1970; Stromberg 1970; Stromberg and Svensson 1971) and has postsynaptic receptor activity (Ungerstedt 1971). PIRIB reportedly elevates NE turnover (Corrodi et al. 1972; Garattini et al. 1974) and at larger doses may act metabolically via presynaptic mechanisms as well as stimulating postsynaptically (Butterworth et al. 1975; Costall and Naylor 1973, 1975; Corrodi et al.

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1972; Goldstein et al. 1973). Thus, these DA agonists each have some neural actions in common and some that differ.

In addition, the present research allowed the examination of biphasic effects, such as low-dose preferential stimulation of autoreceptors that produces inhibitory effects. APO at 0.3 mg/kg, but not at 1.0 mg/kg, caused decreased locomotor activity and frequency of investigation of novel stimuli by gerbils (Cheal 1979), which is analogous to inhibition of locomotor and social behavior by low doses of DA agonists in other species (Carlsson 1975; File 1981; Isaacson et al. 1978; Maj et al. 1972; Stromberg 1970; Thornburg and Moore 1974). However, as there is no single, uniform, biphasic action of DA agonists on behavior, additional DA agonists needed to be tested.

Finally, this paper reports perseveration of investigation following treatment with L-Dopa and PIRIB suggesting an impairment of shift of attention, a behavioral impairment found in humans suffering from schizophrenia (Bleuler 1950; Matthysse 1977).

Materials and Methods

Animals. Male and female Mongolian gerbils (*Meriones unguiculatus*; 84 females, 93 males), born in the laboratory from stock primarily derived from Tumblebrook Farms (West Brookfield, MA), were housed in same-sex groups of 3 – 11 in glass aquaria (31 × 61 × 32 cm) on a 14 h – 10 h light-dark cycle with food and water continuously available. Young adult gerbils (approximately 15 weeks of age, 40 – 95 g) were physically mature and capable of reproduction at the time of testing.

Apparatus. Tests were conducted in a 30 × 45 cm semicircular white plastic arena set into a glass aquarium. The semicircular design, chosen to make the entire arena within the gerbil's visual field (Cheal et al. 1977; Ingle et al. 1979), minimized competing stimuli. A solid black floor was used for the object test and an interchangeable floor with five holes was used for the odor test. The apparatus was washed with water between animals to remove any concentrated areas of animal odor without introducing other, possibly distracting odors. An illustration of the apparatus was published previously (Cheal 1978b).

Procedure. Gerbils were gentled by daily handling for 14 days, placed in the apparatus in groups for 10 min on each of the 3 days preceding the tests, and separately given three adaptation trials prior to testing. This preliminary adaptation reduced the incidence of seizures from 30% – 40% on day 1 to less than 2% on day 5 (unpublished data) and focused investigatory behavior on the novel stimulus (Cheal 1978b; Cheal et al. 1982a). Gentling procedures were used because drugs can have dissimilar effects on adapted and naive animals (Isaacson et al. 1978). The adaptation trials were conducted just as the test trials, except that no stimulus was present. The tests were conducted in the stimulus-elicted investigation paradigm (Cheal 1978b; Cheal et al. 1982a) with 30 – 60 s between trials except where stated otherwise. The drop door was opened, the gerbil ran in: the door was closed and then reopened 60 s later to allow the gerbil to run out. If the gerbil did not readily run through the door, the experimenter gently directed the animal towards the opening.

For the object test, an orange plastic cup, 7.5 cm in diameter at the brim with a 2.5 cm handle, was taped to the wall of the arena. Licking, sniffing, and biting of the cup by the gerbil were recorded by two observers, at least one of whom did not know the drug treatment. The number of approaches was counted and duration was timed with a stopwatch. For the odor test, soiled shavings taken from a cage of adult strange male gerbils were hidden under one of five holes in the floor, counterbalanced across animals. The trials were filmed at four frames per second with a 'Super 8' movie camera. Later, the number of frames in which the gerbil's nose was poked into each hole was counted by an observer who knew neither the hole with the odor nor the drug treatment of the gerbil. From the number of frames, the number of times and the estimated duration of investigation of each hole were obtained. Both frequency and duration measures were recorded as they do not always correlate after neuropharmacological treatment (Cheal 1981). For two trials locomotor activity scores were taken by projecting the film onto a grid and determining the number of line crosses (Cheal 1978a)

Injection and Testing Schedule. Independent groups of gentled, but otherwise naive gerbils were used because behaviors can be conditioned with DA agonists (Cools et al. 1977), and long-term memory is involved in this behavior (Cheal et al. 1982a). All injections were administered SC at the back of the neck on day 1 to eliminate the possibility of different effects due to different sites of injection. The times of testing after injection were based on behavioral reports following similar drug injections in the rat (Butterworth et al. 1975; Costall and Naylor 1973; Maj et al. 1971; Stromberg 1970; Thornburg and Moore 1974) and on preliminary observations of gerbils given PIRIB or L-Dopa in my laboratory.

Experiment 1: Short Intertrial Intervals. Gerbils were injected with 100 mg/kg carbidopa (Merck, Sharp & Dohme, Rahjah, N.J.), 30 min later with 0 ($N = 8$), 3 ($N = 8$), 10 ($N = 8$), 30 ($N = 8$), or 100 ($N = 7$) mg/kg L-Dopa (Sigma, St. Louis, MO). Carbidopa inhibits peripheral decarboxylase and, therefore, intensifies and prolongs the action of L-Dopa, increasing the amount of brain DA while suppressing heart DA (Stromberg 1970; Lotti and Porter 1970). Larger doses were not used because preliminary studies showed that gerbils did not investigate an object if given 300 mg/kg L-Dopa. Five other groups of gerbils were injected with 0 ($N = 6$), 10 ($N = 7$), 30 ($N = 6$), 100 ($N = 6$), or 300 ($N = 6$) mg/kg PIRIB (ET-495, Trivastal; Les Laboratoires Servier, Orleans, France). The drugs were each dissolved in 0.1 N HCl by warming and stirring and then diluted with 0.9% NaCl. Vehicle injections had the same acidity as the most concentrated injections of drug. Larger doses of PIRIB were prohibited by solvency. At 10 min after L-Dopa and 180 min after PIRIB injection, gerbils were given three adaptation trials followed by object-elicited investigation and odor-elicited investigation in the next 30 min, counterbalanced across gerbils in each dose group for PIRIB. For the object test, the gerbils were given five 1-min trials with the cup on the left, and a sixth trial with the cup on the right side of the arena. For the odor test the gerbils were given five trials with strange odor hidden under one of five holes in the floor.

Experiment 2: Long Intertrial Intervals. Gerbils were injected with carbidopa as above, followed 30 min later with 0 ($N = 8$), 10 ($N = 15$), 30 ($N = 16$), or 100 ($N = 16$) mg/kg L-Dopa. Other gerbils were injected with 0 ($N = 8$), 30 ($N = 15$), 100 ($N = 14$), or 300 ($N = 14$) mg/kg PIRIB. Because the 0 mg/kg groups did not differ, the data were

pooled. After the same time intervals as in experiment 1, all gerbils were given three adaptation trials. Within 1 min, half of each drug group was given one 1-min trial with the cup on the left side of the arena. After 24 h all gerbils were given the remaining trials of the test, i.e., those exposed on day 1 received four trials with the cup on the left and one trial with the cup on the right and those not exposed on day 1 received five trials with the cup on the left and one trial with the cup on the right.

Data Analysis. Analyses of variance with repeated measures were computed with the Biomedical Data Program package (Dixon and Brown 1979), analyzing each measure (duration, frequency, activity scores) independently. Only significant effects ($P < 0.05$, two-tailed) are presented. Individual group differences based on a priori hypotheses of habituation were determined by post hoc Tukey tests. Matched *t*-tests were used to determine odor preferences.

Results

Experiment 1: Short Intertrial Intervals

Object-Elicited Investigation. Low doses of L-Dopa and PIRIB resulted in increased duration, but not frequency of responding on trial 1, while high doses of these drugs produced decrements in both measures (Fig. 1A, $P < 0.001$ for each measure for each drug). As in vehicle-treated gerbils, there was a significant trial effect ($P < 0.0001$) that reflected decreased responding with repeated trials indicating habituation and increased responding when the cup was moved for the 0–30 mg/kg groups. Following 100 mg/kg L-Dopa and the higher doses of PIRIB there was no significant decrease on trial 2. Thus, there were significant trial-×-L-Dopa and trial-×-PIRIB interactions ($P < 0.0001$).

Odor-Elicited Investigation. Gerbils given 0–30 mg/kg L-Dopa and all doses of PIRIB investigated the odor hole significantly more than nonodor holes. Following an injection of 100 mg/kg L-Dopa there was no interest in any of the holes on any trial. In addition, following 30 mg/kg L-Dopa there was an increment in duration of responding to the odor on the first trial (Fig. 1B) with no concomitant increase in responding to nonodor holes. Increase in duration of odor investigation was accompanied by significant decrease in number of approaches to the odor hole ($P < 0.05$).

A trial effect ($P < 0.0001$) was due to decrease in responding over trials in 0–30 mg/kg L-Dopa groups and all PIRIB groups, both of investigation of the odor hole and of responding to all five holes.

Activity Score. There was a monotonic decrease in activity with increasing doses of L-Dopa ($P < 0.0001$) or PIRIB ($P < 0.05$) on trial 1 (Fig. 2). Gerbils given 30 or 100 mg/kg L-Dopa or 300 mg/kg PIRIB displayed a variety of abnormal behaviors (stereotypies) in which they were often stationary, but had low startle threshold. Control and low-dose groups responded less on trial 2 than on trial 1 (trial effect $P < 0.001$), but following the two highest doses there was no trial 2 decrease.

Experiment 2: Long Intertrial Intervals

Overall Effects. Data were analyzed for sex, L-Dopa or PIRIB, and exposure condition as grouping variables and six

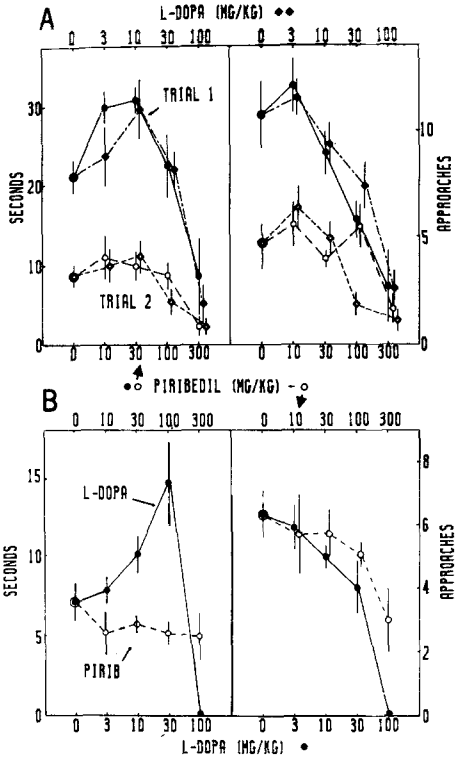

Fig. 1 A, B. Acute effects. Investigation of novel stimuli by gerbils given 100 mg/kg carbidopa and L-Dopa 45–60 min and 15–30 min previously, or PIRIB 185–200 min previously, respectively; mean duration (seconds, *left*) and frequency (approaches, *right*) in experiment 1. Bars show SE. Vehicle data (0 mg/kg) were combined for graphics but were analyzed separately. **A** Responses to a cup, trial 1 (solid symbols), trial 2 (open symbols). **B** Responses to a hole with conspecific odors on trial 1

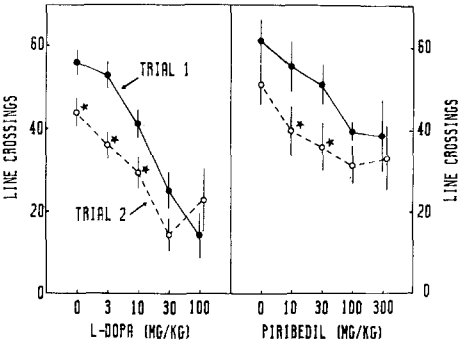

Fig. 2. Locomotor activity. Mean line crossings by gerbils treated with 100 mg/kg carbidopa and L-Dopa (*left*) or PIRIB (*right*). Stars indicate significantly fewer line crossings on trial 2

trials as repeated measures. Significant trial effects ($P < 0.0001$ for each drug) reflected decreased responding for every group over trials and increased responding by every group on trial 6 when the cup was moved.

Trial 1. L-Dopa effects ($P < 0.001$) and PIRIB effects (duration $P < 0.05$, frequency $P < 0.01$) of the exposed group on day 1 replicated trial 1 effects in experiment 1 (Fig. 3A compared to Fig. 1A). There was a small increment in duration of investigation by the 10 mg/kg L-Dopa and the 30 mg/kg PIRIB groups, with no increase in approach frequency. There were large decrements in responses of the

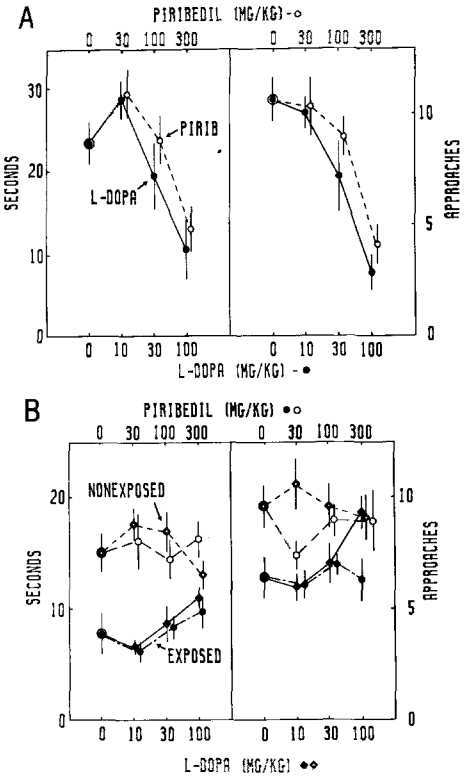

Fig. 3A, B. Long-term effects. Investigation of a cup by gerbils given 100 mg/kg carbidopa and L-Dopa, or PIRIB on day 1; mean duration (seconds, *left*) and frequency (approaches, *right*). **A** Day 1, trial 1, 15 min after L-Dopa (closed symbols) or 185 min after PIRIB (open symbols). **B** Day 2, 24 h after injection of L-Dopa (diamonds) or PIRIB (circles). Trial 1 for gerbils that had never seen the cup before (nonexposed, open symbols) is compared to trial 2 for those who were exposed to the cup on trial 1 following drug injection (closed symbols)

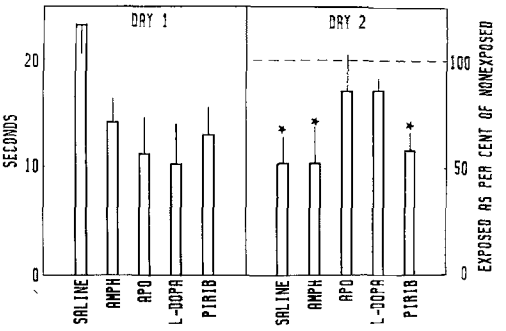

Fig. 4. Object-elicited investigation. Day 1: Duration of investigation of a cup by gerbils given saline, *d*-amphetamine base (AMPH, 1 mg/kg), apomorphine hydrochloride (APO, 1 mg/kg), L-Dopa (100 mg/kg after 100 mg/kg carbidopa), or piribedil (PIRIB, 300 mg/kg). Day 2: Duration of investigation of a cup by the same gerbils 24 h after injection presented as the percent of the duration of investigation by gerbils given the same drug dose treatment, but not exposed to the cup on day 1. Stars indicate significantly less responding by those exposed to the cup on day 1

100 mg/kg L-Dopa and the 300 mg/kg PIRIB groups. Nonexposed gerbils, tested for the first time on day 2, did not show significant dose effects on trial 1 (Fig. 3B).

Day 2. Gerbils given 0, 10, or 30 mg/kg L-Dopa or any dose of PIRIB and exposed to the cup for 1 min on day 1 responded significantly less on day 2 than those gerbils with the same drug treatment who had not seen the cup previously (Fig. 3B). However, there was no effect of day-1 exposure to the cup in those gerbils given 100 mg/kg L-Dopa on day 1. Thus, at this dose, there was no evidence of memory even though these gerbils investigated the cup for a mean of 10.3 s on their first exposure following drug injection. In contrast, memory was evident at every dose of PIRIB.

Discussion

Selective Attention. L-Dopa, but not PIRIB, disrupted selective attention similarly to disruption seen following APO injections (Cheal 1980). To compare effects of DA agonists on these behaviors, drug doses were equated by comparing doses that had similar effects on investigation during the acute phase of drug action (Fig. 4, day 1). Amphetamine (1 mg/kg, Cheal 1980), APO (1 mg/kg, Cheal 1980), L-Dopa (100 mg/kg), and PIRIB (300 mg/kg) each reduced the duration of investigation of a cup on trial 1 to approximately half of control responses. Although no detailed analysis of stereotypy was made in this experiment, these doses of all four DA agonists induced some abnormal stereotypic movements similar to those described for amphetamine (Cheal et al. 1978) and APO (Cheal et al. 1982b). L-Dopa (100 mg/kg) and APO (1–10 mg/kg) resulted in no significant difference between the responses of gerbils exposed to the cup and those of gerbils who were not previously exposed (Fig. 4, day 2). Thus, the 24-h data for O-Dopa and APO are consistent with the lack of a selective response to a novel object on day 1. However, amphetamine (1–6 mg/kg, Cheal 1980) and PIRIB (up to 300 mg/kg) did not disrupt the expression of memory on day 2 even though they had the same depressant effect on investigation on day 1 (Fig. 4).

These DA agonists also differentially affected selective responding to odors. Amphetamine (1 mg/kg, Cheal 1978a) and PIRIB (300 mg/kg) reduced the amount of odor investigation as it did the duration of cup investigation, but there was significantly more investigation of the odor than the nonodor holes; i.e., they demonstrated a preference for the odor. In contrast, L-Dopa (100 mg/kg) and APO (1 or 3 mg/kg, Cheal 1979) virtually eliminated all investigation of the holes and no odor preference was shown at the same doses that reduced cup investigation only about half.

Biphasic Effects of DA Agonists. Both L-Dopa and PIRIB had biphasic effects on duration of cup investigation. However, low doses caused increases in investigation, rather than decreases as seen with APO injections (Cheal 1979). High doses attenuated responding; a nonspecific drug effect caused by any drug at very high doses, such as amphetamine (Cheal 1978a, 1980), APO, pimozide (Cheal 1979, 1980), scopolamine, physostigmine (Cheal 1981), clonidine, and desmethylimipramine (Cheal 1982). The decrement in locomotor activity in this experiment is consistent with decrement in activity following the same high doses of L-Dopa in female mice (Stromberg 1970) and male rats (Maj et al. 1971).

Perseveration. Increased investigation following low doses of L-Dopa and PIRIB suggests perseveration of attention. The increment in responding was not related to locomotor activity because, at these low doses, the correlation coefficients

between activity score and duration of investigation were not statistically significant [L-Dopa r (12) = −0.318, PIRIB r (17) = −0.037]. Responses to odors were not increased by the same doses, but a half-log higher dose of L-Dopa resulted in longer odor investigation. Increased duration with no concomitant increase in frequency induced by L-Dopa and PIRIB support the suggestion that DA agonists might induce an inability to shift attention (Matthysse 1977). Increased duration of investigation has not been seen previously with other drugs in this paradigm, i.e., amphetamine (Cheal 1978a, 1980), APO, pimozide (Cheal 1979, 1980), scopolamine, physostigmine (Cheal 1981), clonidine, or desmethylimipramine (Cheal 1982). However, increased duration of investigation of conspecific odors occurred in male and female gerbils following castration (Cheal and Rezendes 1982). It may be that castration and DA agonists interact in mediation of shift of attention, as has been demonstrated in other behaviors (Chiodo et al. 1979; Menniti and Baum 1981).

Mechanisms of Drug Action. Differential behavioral effects of these four DA agonists may be related to mechanisms of drug action. APO and L-Dopa (100 mg/kg) both disrupt selective attention and are direct receptor stimulants (Ungerstedt 1971) that do not elevate NE turnover (Andén et al. 1967); Everett and Borcherding 1970; Stromberg 1970; Stromberg and Svensson 1971). In contrast, amphetamine and PIRIB, which do not disrupt selective attention, have presynaptic metabolic activity (Andén et al. 1967; Butterworth et al. 1975; Corrodi et al. 1972; Costall and Naylor 1973, 1975; Goldstein et al. 1973) and also act via NE systems (Corrodi et al. 1972; Garattini et al. 1974; Glowinski et al. 1966). On the other hand, low doses of L-Dopa and PIRIB, which cause perseveration, act as prodrugs (Andén et al. 1967; Arana et al. 1983; Costall and Naylor 1975; Everett and Borcherding 1970; Miller and Iversen 1974; Stromberg 1970) and have additional presynaptic metabolic activities (Ahlenius 1974; Butterworth et al. 1975; Corrodi et al. 1972; Costall and Naylor 1973, 1975; Goldstein et al. 1973; Iversen 1977) as well as direct receptor stimulation. Because the appropriate dose of clonidine prevented disruption of selective attention by APO (Cheal 1982), and because of DA-NE interaction in survival-related behaviors (Antelman and Cagguila 1977), it is tempting to stress the importance of the DA-NE interaction.

Perseveration following low doses of L-Dopa and PIRIB could be due to preferential stimulation of presynaptic or autoreceptors. However, low doses of APO that decrease locomotor activity, possibly via presynaptic stimulation, result in decreased investigation, not in perseveration (Cheal 1979, 1980).

Although mechanisms of drug action that result in differing effects on attention can only be speculative due to additional known and unknown actions on other neurotransmitters, different subtypes of attention can be separated both behaviorally and by psychopharmacological manipulation. Thus, the gerbil model provides an extremely useful method for studying problems of attention that occur in schizophrenia and other mental illnesses.

Acknowledgements. Sincere appreciation is given to Dr. R. Baldessarini for his stimulating comments on this work, to E. Bartzokis, A. Fay, L. Gardner, D. Hills, S. Kaloustian, P. O'Glishen, L. Oshry, W. Raimondi, and A. Reed for technical assistance, and to B. Panza for typing the manuscript. The drugs were kindly furnished by Dr. G. Hauser, Dr. R. Baldessarini, and Merck, Sharp and Dohme, Rahway, N.J. The research was supported by the Scottish Rite Schizophrenia Research Program, NMJ, USA and by the Biomedical Research Support Program, DRR, NIH.

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Received July 27, 1982; Final version January 20, 1983