Pharmacology Biochemistry & Behavior, Vol 14, pp 433–438, 1981 Printed in the U.S A

Effects of Chlorpromazine on Escape and Avoidance Responses: A Closer Look

WANEEN W. SPIRDUSO[1] AND LAWRENCE D. ABRAHAM

The University of Texas at Austin

AND

MICHAEL D. WOLF

New York University

Received 14 July 1980

SPIRDUSO, W. W., L. D ABRAHAM AND M. D. WOLF *Effects of chlorpromazine on escape and avoidance responses A closer look.* PHARMAC. BIOCHEM. BEHAV **14**(4) 433–438, 1981.—While a wealth of evidence has implicated the nigrostriatal dopamine system in the initiation of movement, most or all of these movements have been in a conditioned avoidance framework, and on the order of 3–14 seconds in latency It is proposed here that an elucidation of dopaminergic involvement in movement initiation requires a behavioral paradigm wherein experimental animals must rapidly and voluntarily respond to a stimulus to move (i.e., in less than 300 msec, paralleling human reaction time). Such a paradigm was developed and implemented in a re-analysis of earlier reports of chlorpromazine (CPZ) effects on escape from and avoidance of electric shock Catecholaminergic or dopaminergic receptor blocking by CPZ resulted in clear impairment of the ability to initiate rapid avoidance movements, but in contrast to earlier work, some impairment of escape responses was also seen. Results are seen as further support for dopaminergic involvement in the initiation of voluntary movement.

Chlorpromazine Dopamine Movement initiation Conditioned avoidance

THE behavioral effects of chlorpromazine (CPZ) have been described as specific disruptions of motor behavior such as difficulty in "initiating" learned and purposeful movements while not affecting flexor, placing, or righting reflexes [5] or escape responses [7,8]. More specifically, it has been proposed that CPZ delays voluntary movement initiation (e.g. avoidance latency) without affecting locomotion, initiation of escape responses, or movement speed [11, 17, 18].

These CPZ effects are central to a model suggesting that catecholaminergic systems such as the basal ganglia have a role in the initiation of learned movements. The caudate nucleus has been widely linked to the initiation of conditioned or learned responses [2, 3, 5, 9, 10, 11, 12, 14, 15, 20].

More recently, Wolf *et al.* [23] found significantly faster simple voluntary reaction times (RT) in rats with significantly higher caudate dopamine receptor binding affinity (lower K_D). The mechanism involved in the behavioral effect was hypothesized to be a dopamine-influenced selective attention mechanism, independent of motor function, that acted as a filter for irrelevant stimuli [14,16] and produced specific deficits in the initiation of movement rather than in the completion of the entire response. To test this hypothesis one must carefully analyze the initiation of a "voluntary" movement.

Characteristically, escape and avoidance tasks, requiring an animal to move from one shuttle box chamber to another, have been used in studies of purposeful and goal-oriented movements. The onset of shock has been the *unconditioned* stimulus (UCS) and the onset of a warning light or buzzer has been the *conditioned* stimulus (CS). Animals which moved into the safe chamber after the conditioned stimulus (CS; light or buzzer) but before the unconditioned stimulus (UCS; shock) succeeded in avoiding the shock, and those that left the shock chamber subsequent to the onset of the shock were said to escape the shock. CS-UCS intervals typically range from 3 to 15 seconds. The appeal of this technique has been that it provides 60–80% successful avoidances in a very short period of time (usually in one or two test sessions). However, whether the avoidance behavior is scored as the number of trials necessary to reach a criterion, or the latency of the avoidance from the CS to entry into the safe chamber, it is clear that this is a very slow behavioral response, with the potential interaction of many unidentified variables (e.g. locomotor skill, body weight, speed of movement, individual speed preference, exploratory tendencies, spontaneous activity levels, and sensitivity to shock) that primarily affect response completion and not movement initiation. The use of short one- or two-day practice sessions in these long la-

[1]Send reprint requests to W. W. Spirduso, Chair, Dept. of Physical and Health Education, University of Texas, College of Education, Austin, TX 78712.

tency response tasks has amplified both the potential for unwanted variable interaction and ambiguity of response interpretation. The apparent need for a better measure of movement initiation was addressed recently by Wolf [19,20], who shaped avoidance responses to minimal latencies. Response latencies that reveal an animal's reactive capacity rather than its characteristic response style should also provide a more sensitive measure of the effects of CPZ, and consequently would provide a more accurate assessment of catecholaminergic involvement in movement initiation.

The purpose of this experiment, therefore, was to employ a response paradigm in which the animal was systematically shaped over a period of several days to initiate an extremely fast and consistent avoidance consisting only of limb movements and requiring only milliseconds to complete. By using such a short duration response, the effect of different levels of CPZ on the actual initiation of the response could be observed. Additionally, by varying the CS-UCS interval, the effects of CPZ on association and consistency could be ascertained, and interpretations with regard to catecholaminergic involvement in movement initiation could be proposed.

METHOD

Subjects

Thirty-seven male Sprague-Dawley rats (450 to 650 g) were subjects of the study. The animals were obtained from the Charles River Laboratories (Wilmington, Massachusetts), and were individually housed at a constant temperature of 78°F (25°C) with a 12/12 hour light/dark cycle, and ad lib access to standard rat chow and water

Instrumentation and Procedures

Behavioral testing and shaping. Each animal was placed in a standard stainless steel and Plexiglas operant conditioning chamber (Lafayette, Model 84021), which contained a stimulus light, an operant lever, and a shock grid floor. The animal was taught first to maintain the operant lever in a depressed position and then to release it as quickly as possible to the CS (avoidance) or the UCS (escape). An auditory stimulus of 101 dB intensity was paired with the light stimulus, so that the CS was the simultaneous onset of both light and the sound. The UCS was scrambled, constant current electric shock (300 V, 3 mA), well above the animals' thresholds of sensitivity.

Prior to the pre- and post-drug sessions, the animals were conditioned during 50 trials on each of seven days. This shaping schedule included two phases: phase one involved presentation of simultaneous CS and UCS until the animal learned to depress the lever, to hold it in position, and to release it within 180 msec following onset of the shock. The release of the lever opened the circuit and terminated the UCS. This constituted an escape, and generally occurred within 30–50 trials on the first day. The animals quickly adopted a strategy of sitting on their haunches and continuously pressing the bar. Thus when the UCS onset occurred they were in the most efficient position to release the bar quickly. The release of the bar was immediately followed by a depression of the bar. Following five consecutive escapes, phase two, which was the presentation of the four CS-UCS intervals of 1000, 500, 300, and 200 msec, was begun. The long (1000 msec) CS-UCS delay interval was first introduced to enable avoidance responses to occur. When the animal successfully avoided (released the lever within the CS-UCS interval) on 5 consecutive trials, the CS-UCS interval was reduced to 500 msec. Each set of five consecutive successful avoidances, (the criterion for avoidance success) then reduced the CS-UCS interval to the next step until the 200 msec interval was reached. The test session on the seventh day consisted of five zero-delay trials, followed by 10 trials of each of the four CS-UCS intervals. Inter-trial intervals were varied randomly from 27–32 seconds

Experimental Design and Analysis

A 4×3×2 groups-×-interval-×-test session mixed factorial analysis of variance design was used, in which each of four groups received one treatment dose (0.0 (saline)/2.5/3.5/4.5 mg/kg) and was presented with three CS-UCS intervals (500/300/200/msec; see below) in each of two test sessions (pre-drug/post-drug) that was, (a) within the rats' capability to respond, and (b) similar to those used in the study (Poslun [17]) most similar to the present one in terms of purpose. CS-UCS intervals were selected in prior experimentation as being intervals neither too long nor too short, yet differentiating among rats' reactive capacities. Because fewer animals reached avoidance criteria than escape criteria, fewer animals were available for the avoidance analysis

Dependent variables were escape latency, escape latency variability, percentage successful avoidance, avoidance latency, and avoidance latency variability. *Escape latency* was defined as the latency between the simultaneous onset of the CS/UCS and a precise and immediate release of the operant lever. Although escapes also occurred after unsuccessful avoidances in each of the intervals, these were not computed in the analysis as they included anticipatory behaviors. *Escape variability* was the standard deviation of the animal's escapes. *Percent avoidance* was obtained by determining the percent of avoidance responses in the trials provided at each delay interval for each day. *Avoidance latency* was defined as the time between the onset of the CS and the release of the operant lever when it preceded and thus precluded the onset of the UCS. *Avoidance variability* was the standard deviation of the avoidances at each delay interval.

Treatment

The test day was comprised of two test sessions: a pre-drug and post-drug session. In the pre-drug session, consisting of 50 trials, the CS-UCS intervals were provided according to the phase two criteria previously described. Animals were then weighed and injected intraperitoneally with appropriate doses of CPZ (Thorazine). Forty minutes after the injection, the post-drug test session, consisting of 50 reaction (avoidance) trials was administered. Nine animals were also tested six hours following the post-drug session in a 50 trial delayed test session.

RESULTS

The saline group, which served as a control, was uninfluenced on all dependent variables by injection Results and discussion are focussed, therefore, primarily on the statistical results from the CPZ groups.

Escape Latencies

Although each of the drug level groups' mean escape latencies appeared to be slower in the post-drug session, the

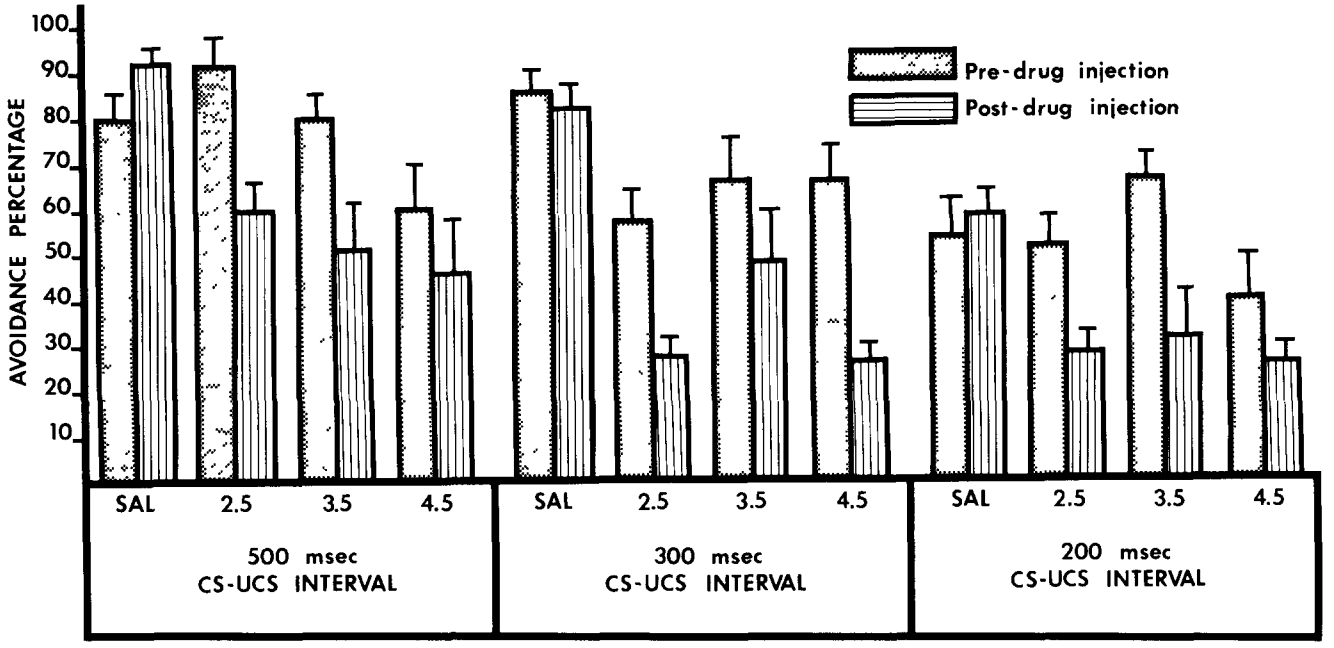

FIG. 1. Pre- and post-drug injection avoidance performance (expressed as percentage of trials on which shock was successfully avoided) The four experimental groups were SAL (saline control N=9), 2.5 (2.5 mg/kg CPZ N=8), 3 5 (3 5 mg/kg CPZ N=9), and 4 5 (4 5 mg/kg CPZ N=10)

drug level main effect from the ANOVA only approached statistical significance, $F(2,23)=2.7$, $p=<0.09$. (For computational details and rationale for using post hoc tests following a nonsignificant overall F test, see Winer [21].) Newman-Keuls post hoc tests computed for each group revealed that the 3.5 CPZ group's mean post injection escape latency of 134.9±40.0 was significantly slower than the preinjection escape latency of 111.9±28.6 (S_B-q 1-$\alpha(2,23)$ $=8.99, p<0.01$). No significant differences were seen in within-animal escape variability.

Avoidance Percentage

The percent of successful avoidance was dramatically affected by injections of CPZ at all levels. Inspection of Fig. 1 reveals that at each drug level the post-drug session percentage was significantly reduced, $F(1,21)=49.3, p=<0.001$. It is also apparent from Fig. 1 that the CS-UCS interval has a significant impact upon the percentage of successful avoidance (the shorter the interval, the smaller the percentage of avoidance; $F(2,42)=14.6, p=<0.001$). No main effects were observed for the level of CPZ, and no significant interactions were observed.

Mean Avoidance Latency

The only significant main effect for latency was the CS-UCS interval effect, $F(2,56)=31.6, p=<0.001$, indicating that the shorter the CS-UCS interval, the faster the response (Fig. 2). Significant interactions were seen in the Test Session×Interval, $F(4,56)=4.9$, $p=<0.01$, and the Drug Level×Test Session×Interval, $F(6,60)=2.7$, $p=<0.05$, interactions. The Drug Level×Interval interactions approached significance, $F(6,56)=2.3, p=<0.08$. More slowing was seen in the longest CS-UCS interval than in the shorter ones, and in the 2.5 and 4.5 CPZ dosage groups than in the 3.5 group.

Consistency of Avoidance

In all but two instances, the within-rat variability (standard deviation of each rat's performance about his own mean) was significantly less after CPZ injection, $F(1,8)=16.2$, $p=<0.01$. In Fig. 3 it can be seen that the shorter the CS-UCS interval (and hence the faster the response), the more consistent the animal's response, $F(2,56)=23.9$, $p=<0.09$. Changes in consistency occurred more in the 3.5 and 4.5 mg/kg groups than in the 2.5 mg/kg group, and more in the slowest interval analyzed, the 500 msec interval.

Delayed Test Session

The nine animals tested again six hours after the Post-drug Session behaved very similarly in both post-drug and the delayed test sessions. No significant differences were seen in avoidance percentage, latency, or variability, nor were escape latencies different. Thus, the effects of CPZ on movement initiation were evident at least six hours after treatment.

DISCUSSION

The results of the study, while supporting previous implications of catecholaminergic systems in movement initiation, clearly indicate that task parameters influence avoidance performance. In this study the most significant evidence of the effect of CPZ is found in the dramatic reduction in avoidance percentage, while the slowing of avoidance

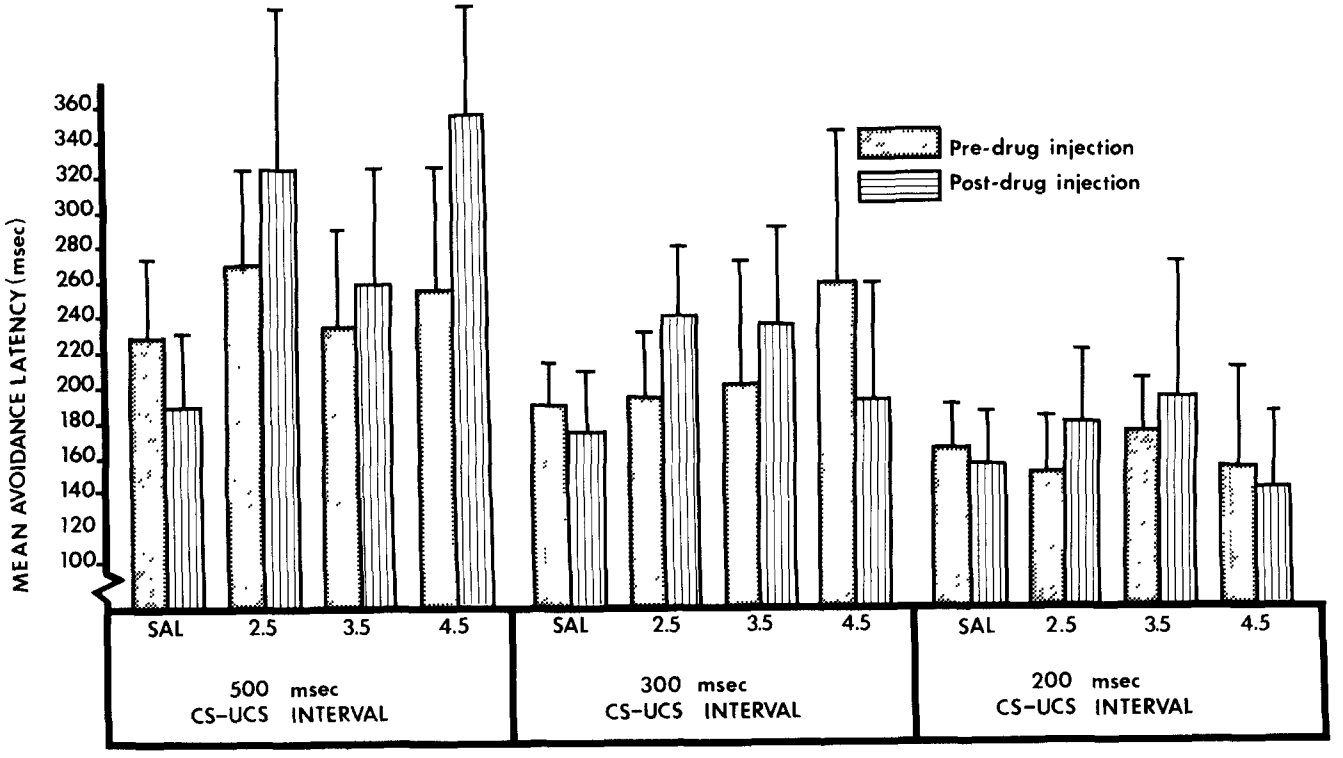

FIG 2 Pre- and post-CPZ mean avoidance latencies in msec. The four experimental groups were SAL (saline control N=9), 2 5 (2 5 mg/kg CPZ N=8), 3 5 (3 5 mg/kg CPZ N=9), and 4.5 (4 5 mg/kg CPZ N=10)

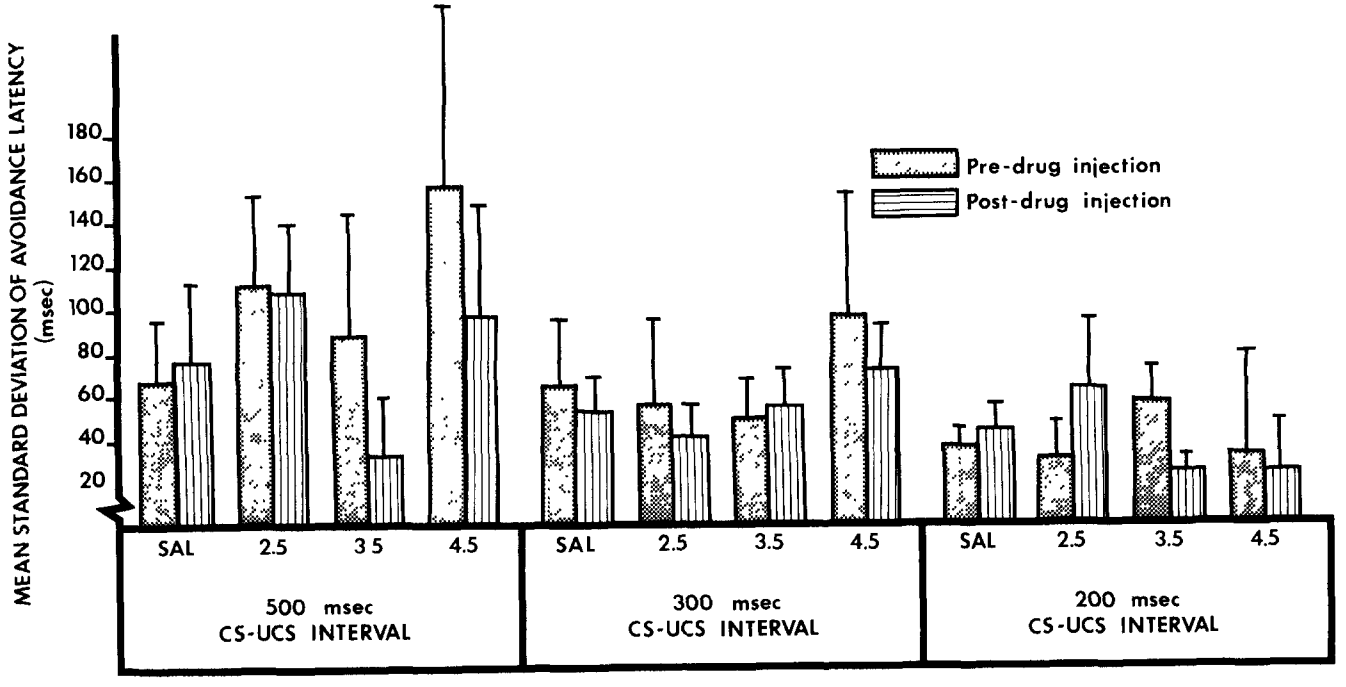

FIG. 3. Pre- and post-CPZ within-subject variability of avoidance performance. The four experimental groups were SAL (saline control N=9), 2 5 (2 5 mg/kg CPZ N=8), 3.5 (3.5 mg/kg CPZ N=9), and 4.5 (4 5 mg/kg CPZ N=10).

latencies was less profound. This is interpreted as being a direct but unavoidable result of the restriction of information processing time by the shorter CS-UCS intervals: since responses must have occurred within 200 msec of CS to be called "avoidances," it would be definitionally very difficult to observe any great degree of CPZ-induced avoidance response slowing. The maximal reactive capacity of the Sprague-Dawleys was approximately 120 msec. This would allow up to 80 msec (approximately) of drug effect on avoidance before the response would have to be defined as an escape. In contrast, since the 500 msec CS-UCS interval allowed more time for a successful avoidance, there was more "headroom" for avoidance response slowing (up to approximately 380 msec). It is not surprising, in light of these points, that successful post-drug avoidances in the 200 msec interval were not slower than pre-drug avoidances, though they were far fewer in number.

The impact of CPZ in the shorter intervals therefore is best shown by the large number of animals that were not able to provide an avoidance in the short intervals, and the smaller percentage of successful avoidances by those animals that provided some avoidances. The important observation is that many responses can be made by many animals just as quickly under CPZ influence as in normal conditions. But the frequency of these behaviors is substantially reduced. Assessment of response consistency is likewise affected by CS-UCS delay interval. Although the overall effect of CPZ was to reduce consistency, the 200 msec delay interval was so close to the animals' reactive capacity that there was little chance for variability in avoidance latency.

Despite the difficulties encountered by using such short CS-UCS delay intervals, their use provided strong support for catecholaminergic involvement in movement initiation, but refuted the suggestion by Poslun [17] that the action of CPZ is selective to the initiation of locomotion and does not affect the acquisition nor the maintenance of a conditioned response such as bar pressing [13]. CPZ appears to impair seriously the maintenance of the initiation of this extremely short duration (15 msec) conditioned manipulatory response.

Response consistency was found to be very high, and response duration was very short. Thus, variability in response execution is more attributable to the internal processes of movement initiation. Even this task, however, does not measure the absolute first components of the response; such evidence of true movement initiation would require a much finer-grained movement analysis.

Analysis of escape performance in this task has yielded ambiguous results. Although post-drug escapes were somewhat slower than pre-drug escapes, only one drug level (3.5) yielded a significant difference. Thus, the classic report of no CPZ effects on escape latency was somewhat supported. The slight evidence to the contrary, suggested by the overall F ratio probability of 0.09 and the significant post hoc test difference in one group, may be attributable to the unique learning, arousal, and attention factors involved in this experimental task. However, it is also possible that the apparent lack of an effect of CPZ on escapes represents an inability of response measurements in previous studies to reveal small changes in the actual initiation of very fast responses.

In summary, these results support the concept of catecholaminergic system involvement in the initiation of an avoidance (learned, voluntary) response. Olmstead *et al.* [15] suggested that catecholaminergic blocking affects responses requiring association of a CS to a UCS more than it affects simple reactions to a noxious stimulus. Wolf [22] argued for dopaminergic involvement in the selective attention process required to trigger simple avoidance responses. Supporting evidence of reaction time (RT) latency dependence on the basal ganglia was offered by Amato *et al* [1]. However, since all of these lines of support implicate neural processes preceding movement execution, it was critical to assess the effect of CPZ on actual movement initiation rather than on response execution.

REFERENCES

1. Amato, G., E. Trouche, D Beaubaton and A. Grangetto The role of the internal pallidal segment on the initiation of a goal directed movement. *Neurosci Lett.* **9:** 159–163, 1978.
2. Battig, K., H. E. Roxvold and M. Mishkin. Comparison of the effects of frontal and caudate lesions on discrimination learning in monkeys. *J comp physiol Psychol* **55:** 458–463, 1962
3. Brust-Carmona, H. and I. Zarco-Coronado. Instrumental and inhibitory conditioning in cats. II Effects of paleocortical and caudate nucleus lesion. *Boln Inst Estud méd biol Univ nac Méx.* **27:** 61–70, 1971.
4 Byck, R. Drugs and the treatment of psychiatric disorders In. *The Pharmacological Basis of Therapeutics,* edited by L. S. Goodman and A Gilman. New York MacMillan Publishing Co , 1975.
5. Carp, J. S. and R. J. Anderson. Sensorimotor deficits produced by phenytoin and chlorpromazine in unanesthetized cats *Pharmac Biochem Behav* **10:** 513–520, 1979
6 Chorover, S. L. and C. G. Gross. Caudate nucleus lesions Behavioral effects in the rat. *Science* **141:** 826–827, 1963.
7 Cook, L. and E Weidley Behavioral effects of psychopharmacological agents. *Ann. N. Y. Acad Sci.* **66:** 740–752, 1957
8 Courvoisier, S., J. Fournel, R. Ducrot, M Kai and P Koetschet. Properties pharmacomiques du chlorhydrate de chloro-3 (dimethylan 3 propyl)-10 phenothazie (4560) *RP Arch of Pharmac Ther* **92:** 305–361, 1953.
9 Dean, W H and G. D. Davis Behavior changes following caudate lesions in rhesus monkey. *J Neurophysiol* **22:** 524–537, 1959.
10 Fibiger, H C., A. G. Phillips and A. P. Zis. Deficits in instrumental responding after 6-OHDA lesions of the nigro-neostriatal dopamine projections *Pharmac Biochem Behav* **2:** 87–96, 1974.
11. Fibiger, H. C., A R. Zis and A G Phillips. Haloperidol-induced disruption of conditioned avoidance responding. Attenuation by prior training or by anticholinergic drugs *Eur J Pharmac.* **30:** 309–314, 1975.
12 Grinberg-Zylberbaum, J., R Prado-Alcalá and H. Brust-Carmona Correlation of evoked potentials in the caudate nucleus and conditioned motor responses. *Physiol Behav.* **10:** 1005–1009, 1973.
13. Hunt, H F. Some effects of drugs on classical (types) conditioning *Ann N. Y Acad. Sci* **65:** 258–267, 1956
14. Oke, A G and R N Adams. Selective attention dysfunctions in adult rats neonatally treated with 6-hydroxydopamine *Pharmac Biochem Behav* **9:** 429–432, 1978
15. Olmstead, C E., J. R Villablanca, R. J Marcus and D L Avery Effects of caudate nucleus on frontal cortex ablations in cats IV Bar pressing, maze learning, and performance *Expl Neurol* **53:** 670–693, 1976

16. Podivinský, F and P Torticollis In. *Handbook of Clinical Neurology Disease of the Basal Ganglia,* Vol. 6, edited by P J Vinken and G. W Bruyn Amsterdam· North Holland, 1968, pp. 567–603
17 Poslun, D. An analysis of chlorpromazine induced suppression of the avoidance response *Psychopharmacology* **3:** 361–373, 1962
18. Price, M. T C. and H. C. Fibiger. Discriminated escape learning and response to electric shock after 6-hydroxydopamine lesions of nigroneostriatal dopamine projections *Pharmac Biochem Behav* **3:** 285–290, 1975
19 Seidler, F. J., W. L. Whitmore and T A. Slotkin. Age-dependence of inhibition of rat brain synaptic vesicle [^{3}H] norepinepherine uptake caused by administration of a single dose of reserpine. Persistance of inhibition in adults but not in neonates. *J. Pharmac exp Ther* **206:** 652–660, 1978.
20. Wauquier, A Basal ganglia Control function in instrumental behavior *Appl Neurophysiol* **42:** 103–105, 1979
21. Winer, B F *Statistical Principles in Experimental Design* New York McGraw-Hill, 1962.
22. Wolf, M. Strain differences in nigrostriatal function and the initiation of movement Unpublished dissertation. The University of Texas, 1979.
23. Wolf, M., R. E Wilcox, W H Riffee and L. D Abraham Strian differences in dopamine receptor function and the initiation of movement *Pharmac Biochem Behav* **13:** 5–7, 1980.