produce waves that could be used for echolocation. Since capillary waves extend at least 6.5 body lengths ahead of the beetle, their reflections might be perceptible from an object directly ahead at a distance of perhaps three body lengths. In addition, the jerky swimming pattern may aid echolocation by producing waves as pulses (*8*). Pulsed waves help to avoid confusion between outgoing and incoming signals and carry away less energy than continuous waves. They usually are used in echolocating devices such as radar and sonar and also are characteristic of the echolocating sounds of animals (*9*).

Two different measures of a beetle's swimming speed may be obtained from wave patterns. One of these is calculated (with Eq. 3) from the wavelength of capillary waves moving at the same speed as the beetle. This condition is met in the region where the waves cross the line along which the beetle is moving. The other measure is calculated (with Eq. 4) from the angle of the vee-shaped wake. A third measure of swimming speed could have been obtained from the wavelength of gravity waves had they been visible in the photographs.

The means of the wavelength method and the wake method are in excellent agreement (0.41 and 0.40 m/sec, respectively) for the 17 beetle photographs to which both methods can be applied. The mean difference between the two estimates for each beetle is 0.04 m/sec. My highest estimate of swimming speed was 0.53 m/sec, although speeds up to 1 m/sec have been measured (*10*). This is a remarkably high speed for so small an animal, and probably few nonflying insects are faster.

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Antiparkinsonian Drugs: Inhibition of Dopamine Uptake in the Corpus Striatum as a Possible Mechanism of Action

Abstract. *A variety of antiparkinsonian drugs are potent, noncompetitive inhibitors of dopamine uptake into synaptosomes in homogenates of rat corpus striatum. Inhibition of dopamine uptake may potentiate the synaptic actions of dopamine in the striatum and could explain the antiparkinsonian effects of these drugs. This hypothesis accounts for several clinical features of Parkinson's disease and predicts compounds which may be new therapeutic agents.*

A variety of drugs are useful in the treatment of Parkinson's disease, including anticholinergic agents, antihistamines, phenothiazines, and sympathomimetics. We report here that several of these drugs are potent inhibitors of dopamine uptake in the corpus striatum.

In most regions of the brain, dopamine serves as a precursor for norepinephrine, but in the corpus striatum (caudate nucleus and putamen), it is the predominant catecholamine and occurs in concentrations 100 times higher than norepinephrine (*1*). Recent evidence suggests a role for striatal dopamine in the pathophysiology of Parkinson's disease. The major neuropathological change in the brains of patients with Parkinson's disease is a degeneration of the substantia nigra, a region which contains the cell bodies of the dopamine-containing neurons that terminate in the corpus striatum (*2*). There is a marked decrease in the striatal dopamine content in brains of patients with Parkinson's disease (*2*). Moreover, recent reports indicate that L-dopa (L-dihydroxyphenylalanine), the metabolic precursor of dopamine, ameliorates the major symptoms of Parkinson's disease (*3*).

Catecholamines can be accumulated into brain tissue by a neuronal membrane transport system as well as by reserpine-sensitive retention in storage granules. The membrane uptake system appears to account for the physiologic inactivation of norepinephrine released at peripheral sympathetic synapses and may play a similar role in terminating synaptic activity of norepinephrine and dopamine in the brain (*4*). The neuronal membrane uptake of catecholamines in the brain can be demonstrated in vivo and in vitro in brain slices, homogenates, and synaptosomes (sheared-off nerve endings) (*5*). Catecholamine uptake in the striatum differs from that in other areas of the brain in its resistance to inhibition by desmethylimipramine (*6*), a potent inhibitor of

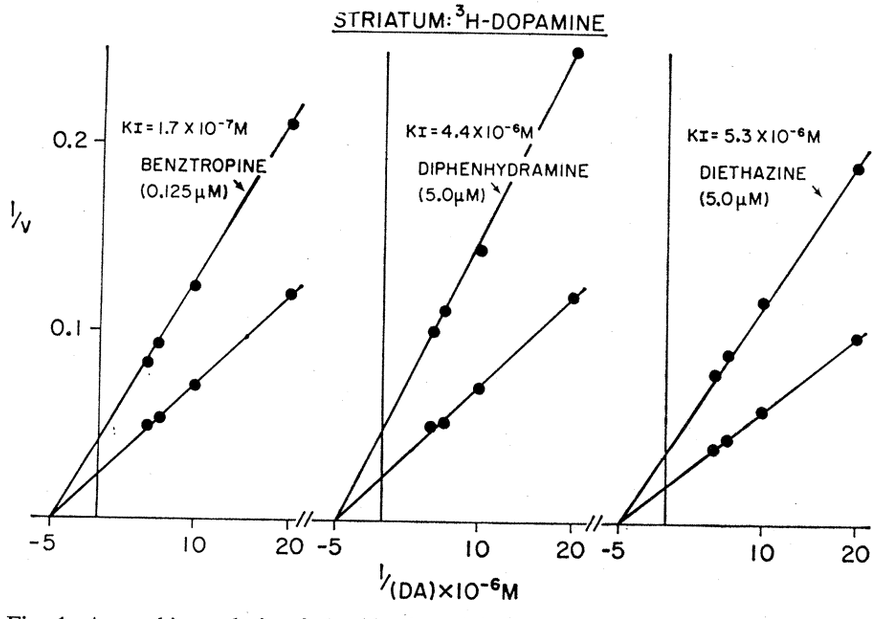

Fig. 1. A graphic analysis of the kinetics of inhibition by benztropine, diphenhydramine, and diethazine of ^{3}H-dopamine uptake into striatal synaptosomes according to the method of Lineweaver and Burk (*8*). Homogenates were incubated in triplicate with concentrations of ^{3}H-dopamine ranging from 0.05 to 0.2 μM and a constant concentration of drug.

Table 1. Inhibition of catecholamine uptake into striatal and hypothalamic synaptosomes by antiparkinsonian drugs. Homogenates from the striatum and the hypothalamus were incubated with drugs ranging in concentrations from $5 \times 10^{-4}M$ to $5 \times 10^{-9}M$ and with 0.1 μM concentration of the respective ^{3}H-catecholamine. Values are presented as the molar concentrations of drugs that produced 50 percent inhibition of ^{3}H-catecholamine accumulation and were determined on logarithmic probability paper. Data presented are the means of three independent determinations for which the standard errors of the means were not greater than 10 percent of the ID_{50} value. Brand names of drugs are in parentheses.

Drug	Corpus striatum, ^{3}H-dopamine (ID_{50} conc.)	Hypothalamus, ^{3}H-norepinephrine (ID_{50} conc.)
Benztropine (Cogentin)	$2.0 \times 10^{-7}M$	$4.0 \times 10^{-6}M$
Trihexyphenidyl (Artane)	$7.0 \times 10^{-6}M$	$4.7 \times 10^{-5}M$
Orphenadrine (Disipal)	$6.0 \times 10^{-6}M$	$4.3 \times 10^{-6}M$
Diphenhydramine (Benadryl)	$4.6 \times 10^{-6}M$	$4.2 \times 10^{-6}M$
Phenindamine (Thephorin)	$4.8 \times 10^{-6}M$	$4.5 \times 10^{-6}M$
Diethazine (Diparcol)	$8.0 \times 10^{-6}M$	$7.8 \times 10^{-6}M$

norepinephrine uptake in nonstriatal brain regions, and in its lack of stereospecificity for the uptake of *d*- and *l*-norepinephrine (*7*).

Male Sprague-Dawley rats (150 to 200 g) received reserpine (2.5 mg/kg of body weight, intraperitoneally) 16 hours prior to decapitation, in order to inactivate the granular storage mechanism for catecholamines and to deplete the animals of the endogenous catecholamines that might exchange with exogenous amine in uptake studies. After decapitation, the striatum (including nuclei of caudate and putamen) was rapidly dissected, weighed, and homogenized in 20 volumes of ice-cold 0.25*M* sucrose. After centrifugation at 1000*g* for 10 minutes, the pellet was discarded and a 0.1-ml aliquot of the supernatant fluid was added to 3.9 ml of modified Krebs-Henseleit (*7*) solution and agitated at 37°C under O_2–CO_2 (95 : 5). After 5 minutes preincubation with varying concentrations of clinically effective antiparkinsonian drugs and $1.25 \times 10^{-5}M$ nialamide to inhibit monoamine oxidase activity, varying concentrations of ^{3}H-dopamine (New England Nuclear, 4.0 c/mmole) or *dl*-^{3}H-norepinephrine (New England Nuclear, 6.6 c/mmole) were added and the incubation was continued for 5 minutes. The incubation mixture then was centrifuged at 48,000*g* for 20 minutes at 4°C, and particulate and supernatant fractions were assayed for tritium. For kinetic studies, velocity was calculated as millimicromoles of ^{3}H-catecholamine accumulated in 5 minutes. Using this technique, we have demonstrated by sucrose density gradient centrifugation and electron microscopic examination of subcellular fractions that ^{3}H-catecholamine accumulated was localized in the synaptosomal fractions of the gradients (*7*). More than 85 percent of the accumulated amine was unmetabolized. Amine uptake was linear for the duration of the incubation and with varying concentrations of tissue homogenates (*7*).

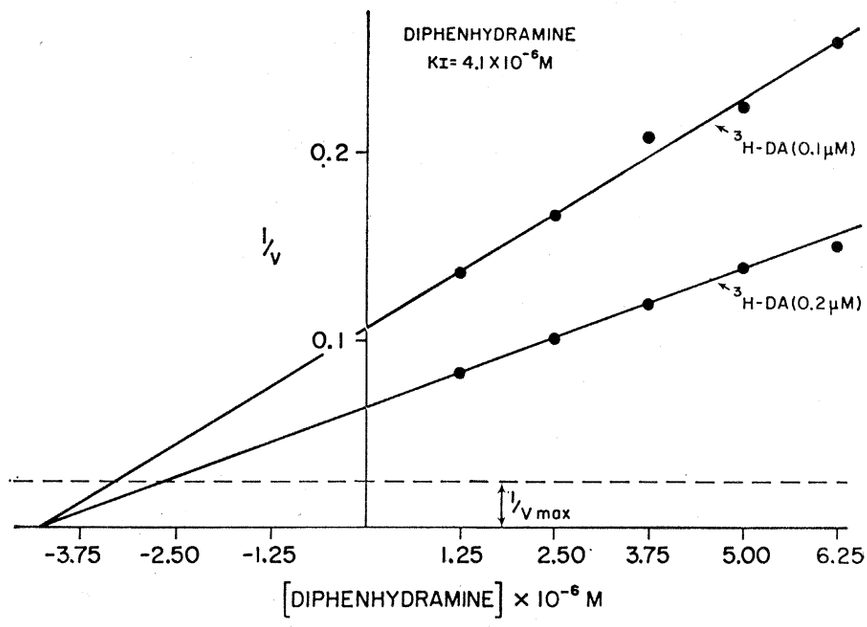

Fig. 2. A graphic analysis of the kinetics of inhibition by diphenhydramine of ^{3}H-dopamine uptake into striatal synaptosomes according to the method of Dixon (*9*). Homogenates were incubated in triplicate with 0.1 or 0.2 μM ^{3}H-dopamine and varying concentrations of drug. The reciprocal of V_{max} was determined by simultaneously measuring the uptake of varying concentrations of ^{3}H-dopamine in the absence of drugs.

The antiparkinsonian drugs examined were potent inhibitors of catecholamine uptake into striatal synaptosomes (Table 1). The most effective inhibitor of dopamine uptake was benztropine, which is one of the most potent antiparkinsonian drugs in man. Although all antiparkinsonian drugs also inhibited hypothalamic norepinephrine uptake, benztropine and trihexyphenidyl were considerably less effective in inhibiting norepinephrine uptake in the hypothalamus than dopamine uptake in the striatum. None of the drugs was markedly more effective in the hypothalamus than in the striatum. This is in marked contrast to the effects of the antidepressant desmethylimipramine and the tranquilizer chlorpromazine. We found that desmethylimipramine was an extremely potent inhibitor of catecholamine uptake into hypothalamic synaptosomes (ID_{50}, $5 \times 10^{-8}M$) but 1000 times less effective in the striatum (ID_{50}, $5 \times 10^{-5}M$). Similarly, chlorpromazine was more potent in the hypothalamus (ID_{50}, $4 \times 10^{-7}M$) than in the striatum (ID_{50}, $8 \times 10^{-6}M$).

In order to determine the nature of the inhibition of catecholamine uptake by antiparkinsonian drugs, we performed kinetic experiments, using the Lineweaver-Burk method (*8*) in which a fixed concentration of drugs was incubated with varying concentrations of catecholamines as well as the procedure of Dixon (*9*) in which drug concentration was varied in the presence of two fixed concentrations of catecholamines (Figs. 1 and 2). With both techniques, the K_i (inhibitory constant) values were similar and were the same as ID_{50} values (Table 1). Inhibition of striatal dopamine uptake was noncompetitive (Figs. 1 and 2), while inhibition of hypothalamic dopamine or norepinephrine uptake by the same drug was competitive (detailed results are in preparation). In an earlier study (*7*) we found that inhibition of ^{3}H-dopamine uptake into striatal synaptosomes by *d*- and *l*-amphetamine was competitive.

The potent inhibition of dopamine uptake into striatal synaptosomes by the

antiparkinsonian drugs examined may be related to the mechanism of their therapeutic activity. Considerable evidence suggests that neuronal uptake of norepinephrine terminates its physiological actions at synapses in the periphery and in the brain (*4*). It is possible that, analogously, the dopamine uptake system in the corpus striatum may inactivate synaptically released dopamine. Tricyclic antidepressant drugs are thought to exert their therapeutic effects by inhibiting norepinephrine uptake at central synapses and potentiating its synaptic actions (*10*). We propose that antiparkinsonian drugs have as a mechanism of action the inhibition of dopamine reuptake, with consequent potentiation of the actions of dopamine released at striatal synapses.

This hypothesis helps explain the clinical observation that patients with increasingly severe Parkinson's disease become progressively refractory to drug therapy. In patients with very severe Parkinson's disease, there would be little dopamine available for potentiation by antiparkinsonian drugs. Antiparkinsonian drugs are more effective in the treatment of drug-induced than idiopathic Parkinson's disease. Patients with the drug-induced syndrome presumably have intact dopaminergic neuronal systems, so that adequate amounts of dopamine are available for potentiation. Recent evidence suggests that phenothiazine drugs that induce Parkinson's disease block dopamine receptors, resulting in enhanced dopamine synthesis and turnover (*11*).

Many antiparkinsonian drugs are also effective anticholinergic agents; and cholinomimetic agents accentuate parkinsonian symptoms (*12*). Thus, it has been postulated that antiparkinsonian drugs antagonize a presumed hyperactivity of cholinergic neurons in the striatum of affected patients (*12*). However, in some studies antiparkinsonian activity failed to correlate with anticholinergic potency (*13*); and amphetamine, which is effective in the treatment of the akinesia and rigidity, exhibits no direct anticholinergic action in therapeutically effective doses. Conceivably, there may be a close interrelationship between cholinergic and dopaminergic mechanisms in striatal neurons, as has been suggested for peripheral noradrenergic neurons (*14*).

We propose that some clinically untried potent inhibitors of striatal dopamine uptake may be useful antiparkinsonian drugs. Such agents might include diphenpyraline, an antihistamine which we found to be a very active inhibitor of striatal dopamine uptake (ID_{50}, $4.9 \times 10^{-7} M$). *d*-Amphetamine has been employed in the treatment of Parkinson's disease, but its central stimulant effects limit dosage. Recently we observed that *d*-amphetamine was ten times more potent than *l*-amphetamine as an inhibitor of catecholamine uptake in nonstriatal brain regions (*7*). However, in the striatum, *d*- and *l*-amphetamine were equally potent and highly effective competitive inhibitors of catecholamine uptake (K_i, $1.0 \times 10^{-7} M$). *l*-Amphetamine, which could be administered in higher doses with fewer central stimulant side effects than *d*-amphetamine, may also be an effective therapeutic agent in Parkinson's disease. In preliminary experiments we examined the effects of these drugs on the tremor and rigidity produced in mice by oxotremorine, a compound that produces a syndrome in animals resembling Parkinson's disease (*15*). As predicted by our hypothesis, *d*- and *l*-amphetamine were equally effective in preventing oxotremorine effects; and diphenpyraline was a highly active anti-oxotremorine agent, almost as potent as benztropine.

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Maternal Influence in Learning by Observation in Kittens

Abstract. *Kittens who observed their mothers perform a stimulus-controlled response (lever pressing to a visual stimulus for food) acquired and discriminated that response sooner than kittens who observed a strange female cat's performance. Kittens exposed to a trial and error condition never acquired the response. Initial differences in attentiveness to demonstrator performances disappeared by the second day. "Altruism" (food sharing) and other forms of social behavior were exhibited by both mother and stranger demonstrators.*

In several animal species, including man, mothers care for their young for a long time after birth. During this time, the young develop sensory and motor functions and acquire skills which are necessary for survival. The mother's role in teaching her young a specific skill, such as acquisition of food, has often been observed (*1*) but has not been experimentally demonstrated. Several investigators have suggested that infant mammals may learn from their mothers (*2*), and from their elders (*3*), primarily by observation. We have previously shown that learning by observation in adult cats is a more efficient method of learning than conventional shaping procedures (*4*). In this study, we undertook to determine whether the speed and efficiency of observation