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# Handling-Induced Seizures and Rotational Behavior in the Mongolian Gerbil

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SCHONFELD, A. R AND S D. GLICK. *Handling-induced seizures and rotational behavior in the Mongolian gerbil.* PHARMAC. BIOCHEM BEHAV. **14**(4) 507–516, 1981.—The aim of this report was to examine the relationship between sensory-induced seizures, cerebral laterality (as measured by rotation) and nigrostriatal asymmetry in Mongolian gerbils. Seizure resistant gerbils made proportionally more spontaneous turns to a preferred direction than sensitive animals Three prototypical antiepileptic drugs strongly elicited rotational behavior (carbamazepine (10–20 mg/kg), diazepam (16 mg/kg) and pentobarbital (40 mg/kg)) and two others (phenobarbital (20–40 mg/kg) and ethosuximide (500 mg/kg)) also appeared to potentiate rotation, only diphenylhydantoin and trimethadione were ineffective. Two dopaminergic agonists, amphetamine (4 mg/kg) and apomorphine (16 mg/kg) enhanced rotation at anticonvulsant doses while the dopaminergic antagonist haloperidol reduced rotational behavior at a dose (1 mg/kg) which exacerbates seizure severity. Finally, surgical induction of nigrostriatal asymmetry by means of unilateral electrolytic striatal lesions reduced seizure severity, sham and bilateral striatal lesions had no significant effects on seizures. These results suggest that seizure activity and rotational behavior are inversely related and, furthermore, that the link between these two behaviors may be the asymmetry between nigrostriatal dopaminergic systems.

Seizures Gerbils Rotation Anticonvulsants

CIRCLING behavior or rotation by rodents has been extensively investigated as a behavioral expression of cerebral functional asymmetry [13]. Although earlier work focused on rotation elicited by surgical, electrical or pharmacological means, more recent observations in our laboratory have revealed that normal, intact rats and gerbils spontaneously rotate [13,20]. Neurochemical analyses indicated that asymmetries exist in striatal dopamine content [12,20] and striatal dopamine metabolism and dopamine-stimulated adenylate cyclase activity [22] which can be correlated with rotational behavior; furthermore, these asymmetries can be potentiated pharmacologically by drugs which stimulate rotation, such as amphetamine. This normal, intrinsic nigrostriatal asymmetry is believed to be responsible for a persistent behavioral lateral bias of the rodent which can be measured as rotation [13].

Myslobodsky and Rosen [34] recently reported that a convulsant (pentamethylenetetrazol) produces asymmetric wave-spike discharges and that rats rotate contralateral to the hemisphere with the lower amplitude discharges. The authors postulate that the intrinsic nigrostriatal dopaminergic asymmetry which underlies drug-induced rotation in nonlesioned rats [11] also modulates the observed asymmetric seizure activity. Since the nondrugged and nonlesioned Mongolian gerbil spontaneously rotates [20] and is susceptible to handling-induced seizures [47], the aim of the present study was to determine what relationship exists between seizures, rotation and nigrostriatal asymmetry by taking advantage of the unique neurological characteristics of the gerbil.

In Experiment 1, in order to determine if seizure susceptibility is associated with altered behavioral laterality, the spontaneous rotational behavior of seizure sensitive gerbils was compared to that of resistant animals. The results suggest that seizure resistant animals are more lateralized (i.e. they make proportionally more rotations to one direction) than sensitive gerbils.

In Experiment 2A, the effects of 7 prototypical anticonvulsant drugs on rotation were determined in order to test the hypothesis suggested in Experiment 1 that seizure resistance is associated with enhanced rotation. We have previously reported on the effects of these drugs on handling-induced seizures in gerbils [44]. To evaluate whether potentiating rotation reduces seizure activity, in Experiment 2B the dose/response effects of drugs which modulate rotation were compared with their previously determined effects on seizure activity [44].

Finally, in Experiment 3 the results of surgical modification of nigrostriatal asymmetry on the seizure behavior of

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susceptible gerbils are described. The results generally support a relationship between enhanced rotation and seizure resistance, although all pharmacological anticonvulsant activity cannot be simply attributed to changes in such asymmetry.

## GENERAL METHOD

### *Subjects*

In all experiments, naive female Mongolian gerbils (*Meriones unguiculatus*) approximately 3 months old (Tumblebrook Farm, West Brookfield, MA) were housed in pairs and supplied with food and water ad lib. Subjects for rotational testing were maintained on a 12-hr light-dark cycle (L/D:7:00 a.m./7:00 p.m.) and tested in the morning. However, because seizure activity is subject to circadian fluctuations [44], unlike rotational behavior [45], subjects for seizure testing were habituated to a reversed lighting schedule (D/L:7:00 a.m./7:00 p.m.) and tested between 9 a.m. and 1 p.m. in order to maximize the probability of observing seizure activity.

### *Seizure Testing*

In Experiments 1 and 3, gerbils were screened for their susceptibility to handling-induced seizures. For this, animals were not handled for at least 1 week prior to testing. Cages were then removed individually from the storage room to the testing room with a minimum amount of disturbance or noise. The seizure test consisted of 2 parts and was an adaptation of the "triple-handling" technique of Cox and Lomax [5]. First, the animal was placed on the top of a laboratory cart and allowed free movement for 2.5 min. The animal was then handled vigorously for 20 sec. The initiation procedure was terminated at the first appearance of seizure activity and the animal was left undisturbed until the seizure had been completed and preictal behavior had returned.

The seizure severity rating scale used was the 7-point scale described fully by Loskota, Lomax and Rich [29]. In summary, the seizures are classified: grade 0, no seizure, grade 1, subject moving with vibrissae and pinnae twitching; grade 2, motor arrest with twitching of vibrissae and pinnae; grade 3, motor arrest with myoclonic jerks followed by "quick release", grade 4, clonic-tonic seizure with prolonged postictal recovery period; grade 5, clonic-tonic seizure with body roll-over and prolonged recovery period; and grade 6, seizure progressing to death.

### *Rotation and Activity Testing*

In Experiments 1 and 2, hourly rotational behavior was measured in opaque spherical Plexiglas rotometers [16]. A flexible wire, which harnessed the animal, was connected to a shaft which activated a photoelectric position sensing device that differentiated between incomplete and full (360°) rotations. Total hourly 360° rotations to the left and right and 90° turns to the left and right were recorded on Sedeco print-out counters.

Two indices of rotation were calculated. the number of "Net Rotations" (i.e. 360° turns in the dominant direction minus 360° rotations in the opposite direction) and "Dominance" (i.e. 360° rotations to the dominant direction/total 360° rotations). At the same time, the number of "Extra Quarter Turns" (i.e. total left and right 90° turns minus 4×total left and right 360° turns) was determined as a measure of random locomotor activity as distinguished from rotatory behavior [16]. In addition, the locomotor activity of the subjects was also measured in Lehigh Valley photocell activity cages (No. 145-03) for 30 min immediately following the rotation session.

Linear regression analyses were used to determine associations between the two indices of rotation and activity. Differences in rotation and activity were analyzed by unpaired Student's *t* tests. Drug effects on rotation and activity were evaluated by computing one-way analyses of variance, unpaired Student's *t* tests and the Duncan's Multiple Range test. Effects on seizure magnitude were analyzed by the use of the Wilcoxon signed ranks test and effects on seizure frequency were evaluated by the Chi-square test.

TABLE 1

ROTATION AND ACTIVITY OF SEIZURE SENSITIVE AND RESISTANT GERBILS

| | Mean | S.E M |
|---|---|---|
| Net Rotation | | |
| Sensitive | | |
| (N=32)* | 31 19 | 4 00 |
| Resistant | | |
| (N=29)* | 29 63 | 3.40 |
| Dominance | | |
| Sensitive | | |
| (N=32) | 0 668 | 0 01 |
| Resistant | ‡ | |
| (N=29) | 0 713 | 0 02 |
| Extra Quarter Turns | | |
| Sensitive | | |
| (N=32)† | 232 58 | 15 00 |
| Resistant | | |
| (N=30) | 210.80 | 20 60 |
| Photocell Counts | | |
| Sensitive | | |
| (N=17) | 1583 31 | 132.53 |
| Resistant | | |
| (N=18) | 1284 82 | 75.20 |

*Subjects not rotating (net rotation=0 or 1) were omitted from the net and dominance calculations (n=2 sensitive, n=1 resistant)

†Subjects (N=2) making more than 3 standard deviations from the mean were excluded

‡Significantly different from each other at $p<0$ 05, *t* test

## EXPERIMENT 1

### METHOD

Gerbils were seizure tested on Monday morning. Fifteen minutes after completion of the seizure test, subjects were placed in rotometers for 60 min. Rotational testing was repeated on Wednesday and Friday mornings. Seizure testing was not repeated since the effects of both postictal refractoriness [28] and prior handling only 2 days before the next test [47] would minimize the likelihood of seizure occurence.

### RESULTS

Thirty-four seizure sensitive and 30 resistant gerbils were tested. The median seizure score was 2 5

TABLE 2

THE EFFECT OF ANTICONVULSANT DRUGS ON ROTATION, ACTIVITY AND SEIZURES IN GERBILS

| Drug mg/kg | N | Rotation | | Activity | | Seizures [44] | |
|---|---|---|---|---|---|---|---|
| | | Net | Dominance | Extra Quarter Turns | Photocell Counts | Seizure Score | Percent Seizing |
| Diphenylhydantoin | | | | | | | |
| Vehicle | 6 | 27.5±11 03 | 0 72±0 07 | 146 8± 17.32 | 808.0±113.90 | 2 0 | 53 |
| 25 | 6 | 22.3± 8.57 | 0.64±0.03 | 185.7± 27.61 | 1290.7±119.77 | 2.0 | 58 |
| 75 | 6 | 39 0±14.18 | 0.69±0 04 | 225.0± 49.60 | 935 7±140 13 | 0.0 | 44 |
| 150 | 6 | 24.7± 8 58 | 0 62±0.04 | 265 7± 37 10* | 1675 3±252.01* | 0.0§ | 15# |
| Phenobarbital | | | | | | | |
| Vehicle | 14 | 39.9± 8 78 | 0.68±0 03 | 204.5± 18 02 | 1216.3± 53 99 | 1.0 | 50 |
| 20 | 12 | 67.9±14.64 | 0.68±0.03 | 353.9± 24.63‡ | 2079.7±152 19‡ | 0.0¶ | 05# |
| 40 | 12 | 73.6±11 73 | 0 66±0.03 | 398 2± 78.35† | 3302 4±283 85‡ | 0 0¶ | 00** |
| 80 | 6 | 52.7±20.90 | 0.65±0 04 | 219 8± 42 74 | 2376 0±381 41‡ | 0 0¶ | 00** |
| Pentobarbital | | | | | | | |
| Vehicle | 14 | 39.9± 8.78 | 0.68±0 03 | 204 5± 18.02 | 1216 3± 53.99 | 1.0 | 50 |
| 20 | 5 | 69.8±23.92 | 0.71±0.08 | 347.4± 73.76* | 1447 3±172 55 | 0.0 | 08# |
| 40 | 6 | 93.0±32.32* | 0.76±0.06 | 449.7±113 64† | 2025.5±508.94 | 0.0§ | 00# |
| Trimethadione | | | | | | | |
| Vehicle | 8 | 26.1±10.67 | 0.66±0.04 | 150.6± 19.26 | 1060 9± 97.01 | 0.0 | 31 |
| 150 | 6 | 37 5± 6 30 | 0 70±0.04 | 261.7± 32.36 | 1486.7±208.80 | 0.0 | 44 |
| 300 | 6 | 20.2± 3.35 | 0.67±0.03 | 161.8± 19.87 | 1075.2±185.56 | 0.0 | 44 |
| 450 | 6 | 29.8± 9.78 | 0.67±0.06 | 258.2± 45 69 | 1724.0±216.04† | — | — |
| 600 | 6 | 34.8±10.19 | 0.65±0.03 | 366.7± 97 68* | 1822.0±353.49* | 0.0 | 31 |
| Ethosuximide | | | | | | | |
| Vehicle | 8 | 18.8± 2.65 | 0 75±0.02 | 141 8±23 33 | 1469.0±104.41 | 2.0 | 56 |
| 125 | 6 | 16.5± 0.72 | 0.72±0.08 | 211.5±48 30 | 1687 5±127.12 | 3.0 | 63 |
| 250 | 6 | 34.5±17.94 | 0.72±0.07 | 159.2±44 33 | 1455 7±155.24 | 0.0 | 44 |
| 500 | 6 | 42.3±14.89 | 0 73±0 05 | 195.3±81.99 | 1777.5±194.65 | 0.0§ | 06** |
| 1000 | 6 | 9.0± 3.92 | 0.82±0 10 | 27 7±10 78† | 761.7±255.82* | — | — |
| Carbamazepine | | | | | | | |
| Vehicle | 8 | 17.8± 3.87 | 0.67±0.03 | 206.1±31.3 | 1376.1± 94.11 | 0.0 | 11 |
| 5 | 6 | 19.3± 6 23 | 0.66±0 04 | 160 5±20.8 | 1910.0±165 80* | 0 0 | 11 |
| 10 | 6 | 34.8± 7.13* | 0 73±0 06 | 165 7±40.2 | 1338.7±168 97 | 0 0 | 00 |
| 20 | 6 | 42.0± 7.65* | 0 72±0 03 | 156 0±19.6 | 1400.2±167.54 | 0 0 | 00 |
| 40 | 6 | 23 2± 3 61 | 0.69±0 04 | 90.0±14.8* | 1766 0±206.69 | 0.0 | 16 |
| Diazepam | | | | | | | |
| Vehicle | 14 | 16 3± 4 11 | 0.65±0.03 | 225 8±35 48 | 1476 9±116.54 | 0.0 | 10 |
| 1 | 6 | 21 3± 9.35 | 0.70±0.06 | 155 5±13 32 | 1931.3±140.66 | — | — |
| 2 | 6 | 16 2± 2 97 | 0 71±0 05 | 134.2±27 59 | 1607 2±113 79 | 0.0 | 10 |
| 4 | 6 | 28 0±17 15 | 0.67±0.07 | 131 3±24 35 | 2261.0±217.11* | — | — |
| 8 | 6 | 23.8± 7.26 | 0.70±0.06 | 160 8±23 88 | 2442.5±224.00‡ | 0 0 | 10 |
| 16 | 16 | 42.9± 7 48† | 0.74±0.03* | 206.8±32 87 | 2602.3±223.88‡ | 0 0 | 00 |

*Significantly different from control, $p<0.05$, $t$ test
†Significantly different from control, $p<0.01$, $t$ test
‡Significantly different from control, $p<0.001$, $t$ test
§Significantly different from control, $p<0.05$, Wilcoxon Signed Ranks test.
¶Significantly different from control, $p<0.01$, Wilcoxon Signed Ranks test
#Significantly different from control, $p<0.05$, Chi square test.
**Significantly different from control, $p<0.01$, Chi square test.

The results are indicated in Table 1. For both groups, the two indices of rotation, net and dominance, were significantly correlated (sensitive: r=0.49, n=32, $p<0.01$; resistant: r=0.62, n=29, $p<0.001$, linear regression analyses) as were the two indices of activity, extra quarter turns and photocell counts (sensitive: r=0.50, n=18, $p<0.05$; resistant: r=0.63, n=19, $p<0.01$). Seizure sensitive subjects displayed significantly less dominance overall than resistant gerbils ($t=2.11$, df=59, $p<0.05$, $t$ test). Differences between groups in both overall extra quarter turns and photocell counts suggested that seizure sensitive gerbils were more active than resistant subjects although these differences did not reach statistical significance (photocell counts: $t=1.97$, df=32, $p<0.10$, $t$ test).

## EXPERIMENT 2A

### METHOD

Seven prototypical anticonvulsant drugs were tested for their effects on rotation and activity. The drugs tested, doses, vehicle solution and number of subjects tested per dose were as follows: (1) Diphenylhydantoin: 25, 75 and 150 mg/kg, sterile water; n=6; (2) Phenobarbital: 20 (n=12), 40 (n=12) and 80 (n=6) mg/kg; vehicle of 50% sterile water, 40% propylene glycol, 10% ethanol (n=14); (3) Pentobarbital: 20 (n=5) and 40 (n=6) mg/kg; same vehicle as for phenobarbital (n=14); (4) Trimethadione: 150, 300, 450 and 600 mg/kg; sterile water (n=8); (5) Ethosuximide 125, 250, 500 and 1000 mg/kg (n=8); sterile saline (n=8), (6) Carbamazepine: 5, 10, 20 and 40 mg/kg (n=6), 70% propylene glycol (n=8); (7) Diazepam: 1, 2, 4, 8, 16 and 32 mg/kg (n=6); 1% Tween 80 in saline (n=14). Forty-five minutes after drug administration, animals were placed into the rotometers for a 15 min habituation period and rotation was monitored for the next hour. All drugs were injected intraperitoneally in a 0.2 ml injection volume. Vehicle solutions were used as controls.

Since many types of sudden movements may stress gerbils and initiate seizures [23], drug administration was conducted in the storage room only by one of the researchers (A.R.S.) who acquired a method of handling and injection using a few deliberate, rapid steps which rarely triggered seizure activity (<2%). Any animal which seized during drug administration was eliminated from the study.

### RESULTS

The effects of anticonvulsant drugs on rotation and activity in gerbils are indicated in Table 2. Diphenylhydantoin had no significant effects on net rotation or dominance; however, at 150 mg/kg DPH increased activity ($p<0.05$, $t$ tests) as measured both as extra quarter turns, $F(3)=2.13$, $p=0.11$, and photocell counts, $F(3)=5.50$, $p<0.01$.

At 40 mg/kg of phenobarbital, net rotation was at a very high level (approximately 75 net rotations/hr), however, this was not statistically significant from control ($t=2.04$, df=20, $p<0.10$, $t$ test). As seen in Fig. 1 which illustrates the effect of the vehicle solutions on net rotations, the barbiturate vehicle solution alone produced significantly more net rotations than any other vehicle ($p<0.05$, Duncan's Multiple Range test). Therefore, the statistical significance of the increased rotation produced by the drug is somewhat masked by an elevated baseline. Phenobarbital increased the number of extra quarter turns $F(3)=4.75$, $p<0.01$ at 20 ($p<0.001$) and 40 mg/kg ($p<0.01$, $t$ tests) and produced significant increases in photocell counts $F(3)=19.33$, $p<0.0001$ at all doses tested ($p<0.001$, $t$ tests). The other barbiturate tested, pentobarbital, enhanced rotation at 40 mg/kg $F(2)=2.44$, $p=0.11$ ($p<0.05$, $t$ test). Pentobarbital increased the number of extra quarter turns $F(2)=5.38$, $p<0.05$ at 20 ($p<0.05$) and 40 mg/kg ($p<0.01$, $t$ tests) and elevated photocell counts $F(2)=3.04$, $p=0.07$ at 40 mg/kg ($p<0.05$, $t$ test).

Ethosuximide had no significant effect on rotation when measured for the entire 1 hr session. However, within only the first 30 min of testing, ethosuximide potentiated net rotation $F(4)=2.59$, $p=0.056$ and increased extra quarter turns $F(4)=2.69$, $p=0.049$. Therefore, these results indicate that the maximal effect of ethosuximide on rotation might have occured during the 1 hr injection/test interval.

Trimethadione had no significant rotatory effects although the drug increased activity as measured both by extra quarter turns $F(4)=3.28$, $p<0.05$ at 600 mg/kg ($p<0.05$, $t$ test) and photocell counts $F(4)=2.77$, $p<0.05$ at 450 ($p<0.01$) and 600 ($p<0.05$, $t$ tests) mg/kg. Carbamazepine enhanced net rotation $F(4)=3.38$, $p<0.05$ at 10 and 20 mg/kg ($p<0.05$, $t$ tests) without significantly affecting activity at these same doses. At 16 mg/kg only, diazepam increased net rotation $F(6)=1.58$, $p=0.17$ ($p<0.01$, $t$ test) and dominance $F(6)=0.74$, $p=0.62$, ($p<0.05$, $t$ test). Diazepam increased photocell counts $F(6)=5.94$, $p<0.001$ at 4 ($p<0.05$), 8, 16 and 32 ($p<0.001$, $t$ tests) mg/kg.

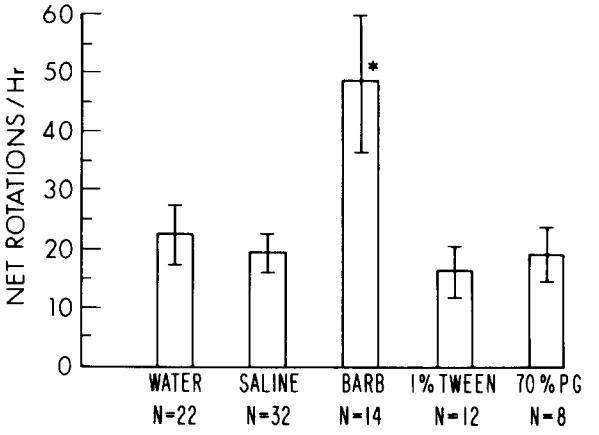


FIG 1 The effect of vehicle solutions on net rotation in gerbils. BARB =Barbiturate vehicle (40% Propylene Glycol, 10% Ethanol, 50% Water). 70% P.G.=70% Propylene Glycol *Significantly different from all other groups ($p<0.05$), Duncan's Multiple Range Test Bars represent±S E M

In summary, three prototypical anticonvulsant drugs clearly enhanced rotation in the gerbil: carbamazepine, diazepam and pentobarbital. In addition, the results suggest that phenobarbital and ethosuximide also stimulate rotation. Increased rotational behavior was not necessarily associated with increased activity (i.e. carbamazepine) and 2 drugs which stimulated activity had no rotational effects (i.e diphenylhydantoin and trimethadione)

For comparison, Table 2 also presents the results of a previous study in which these drugs were evaluated for their effects on handling-induced seizure activity in gerbils [44]. At doses which enhanced rotation, seizure activity was reduced by pentobarbital, phenobarbital and ethosuximide Since the vehicles of both carbamazepine and diazepam decreased seizures, the anticonvulsant properties of these drugs could not be evaluated statistically; however, for carbamazepine and diazepam, seizure activity was completely suppressed at only those doses which stimulated rotation. The results for diphenylhydantoin indicate that anticonvulsant activity is not always associated with increased rotation. In addition, anticonvulsant activity is not simply a result of hyperactivity, as illustrated by trimethadione.

## EXPERIMENT 2B

### METHOD

Four drugs affecting dopaminergic neuronal systems were tested using the same paradigm described for 2A. The drugs tested, doses, vehicle solution, number of subjects and injection/test intervals were: (1) Amphetamine: 0.5, 1, 2, 4, 8

TABLE 3

THE EFFECT OF DOPAMINERGIC DRUGS ON ROTATION, ACTIVITY AND SEIZURES IN GERBILS

| Drug mg/kg | N | Rotation | | Activity | | Seizures [44] | |
|---|---|---|---|---|---|---|---|
| | | Net | Dominance | Extra Quarter Turns | Photocell Counts | Seizure Score | Percent Seizing |
| Amphetamine | | | | | | | |
| Vehicle | 12 | 20 8± 5 30 | 0.68±0.04 | 150.5± 12.97 | 1406 0± 84 21 | 3 0 | 63 |
| 0.5 | 6 | 27 8±10.56 | 0.69±0.07 | 214 0± 39.41 | 1627 0±153 87 | — | — |
| 1 | 6 | 21 0± 5 79 | 0.70±0.06 | 263.3± 42 31† | 1778 0±127.65* | 2 5 | 61 |
| 2 | 6 | 51.0±21 24 | 0 69±0 07 | 232.7± 80 64 | 1556 5±208 43 | 3 0 | 74 |
| 4 | 6 | 83 3±19 41‡ | 0 83±0 06* | 236.3± 58 72 | 2098 8±252 90† | 0 0§ | 39 |
| 8 | 6 | 90 7±28 84† | 0 73±0 06 | 466.3± 90 45‡ | 2191 3±298 90† | 2 0 | 53 |
| 16 | 6 | 92 2±21 29‡ | 0 74±0 05 | 592.3±140 25‡ | 2261 8±230 50‡ | — | — |
| Apomorphine | | | | | | | |
| Vehicle | 8 | 14 6± 1 67 | 0 66±0.05 | 116 3± 12.08 | 1296 3± 98.52 | 2.0 | 58 |
| 2 | 6 | 17 7± 3 08 | 0 62±0 04 | 177.8± 36 29 | 1708 8±103 00* | 0 0 | 35 |
| 4 | 6 | 21 5± 3.18 | 0 68±0 06 | 168.0± 40 01 | 1480 8±114 13 | 0 0 | 45 |
| 8 | 6 | 23 5± 3.66 | 0.68±0.06 | 161.0± 32 72 | 1789 5±167 60* | 0 0 | 28 |
| 16 | 6 | 110.2±12.51* | 0.90±0 05* | 75.3± 12 52* | 1563 7±215 68 | 0 0§ | 21** |
| Haloperidol | | | | | | | |
| Vehicle | 8 | 25 9± 8 11 | 0 80±0 06 | 110.0± 21 93 | 1103 9± 60 66 | 0.0 | 37 |
| 0.5 | 6 | 13 3± 6 01 | 0 68±0 06 | 83.7± 25 95 | 754 8±133 69* | 0 0 | 42 |
| 1 | 6 | 13 3± 3.70 | 0.62±0.03 | 134.7± 24.03 | 948 8±154 46 | 3 0¶ | 53 |
| 2 | 6 | 6 8± 2.54 | 0.73±0 07 | 55.2± 11 28 | 496 3± 93 09† | 3 0 | 53 |
| 4 | 6 | 6 2± 1 05 | 0 68±0 02 | 53.8± 12 55 | 764 7±138 84* | 0 0 | 42 |
| Alpha-methyl-para-tyrosine | | | | | | | |
| Vehicle | 6 | 17.5± 7 29 | 0 70±0 05 | 115 7± 21.26 | 1449 7±172 68 | 4 0 | 81 |
| 75 | 6 | 15 0± 3 72 | 0 69±0.06 | 186 5± 23.02* | 1582.8±196 96 | 4 0 | 79 |
| 150 | 6 | 21 3±10 01 | 0 72±0.07 | 145 0± 16.27 | 1594.7±190 86 | 4 0 | 76 |
| 300 | 6 | 5.7± 2 69 | 0 59±0.05 | 122 7± 12 45 | 1609.5±100 87 | 3 0 | 71 |

See Table 2 for explanation of footnotes

and 16 mg/kg (n=6 per dose); sterile saline (n=12); 30 min; (2) Apomorphine: 2, 4, 8 and 16 mg/kg (n=6 per dose); sterile water (n=8); 30 min; (3) Haloperidol: 0.5, 1, 2 and 4 mg/kg (n=6 per dose); sterile water (n=8); 30 min; and (4) Alpha-methyl-para-tyrosine (AMPT): 75, 150 and 300 mg/kg (n=6 per dose); sterile saline (n=6), 75 min.

When testing amphetamine, apomorphine or haloperidol, gerbils were first placed into rotometers, allowed a 15 min habituation period and tested for rotation and activity (extra quarter turns) during the following 60 min. Immediately after this, gerbils were monitored in the photocell cages for 30 min. For AMPT, subjects were placed into the rotometers for a 15 min habituation period 60 min after drug injection.

## RESULTS

The effects of drugs with dopaminergic activity on rotation and motor activity are presented in Table 3. Amphetamine stimulated net rotation $F(6)=4.04$, $p<0.01$ at 4 ($p<0.001$), 8 ($p<0.01$) and 16 ($p<0.001$, $t$ tests) mg/kg. Dominance was increased significantly at only 4 mg/kg $F(6)=0.81$, $p=0.57$ ($p<0.05$, $t$ test). Amphetamine also enhanced locomotor activity when measured either as extra quarter turns $F(6)=5.68$, $p<0.001$ or photocell counts $F(6)=3.64$, $p<0$ 01.

At 16 mg/kg only, apomorphine increased net rotation $F(4)=7.80$, $p<0.001$ ($p<0.01$, $t$ test) and dominance $F(4)=4.66$, $p<0.01$ ($p<0$ 01, $t$ test). At this dose, apomorphine inhibited extra quarter turns $F(4)=2.31$, $p<0.08$ ($p<0.05$, $t$ test).

When measured during the entire 60 min test session, haloperidol had no significant effect at any dose on net rotation $F(4)=2.26$, $p<0.08$ although dominance was significantly decreased at 1 mg/kg $F(4)=1.74$, $p=0.17$ ($p<0.05$, $t$ test, see Table 3). Haloperidol depressed activity when measured either as extra quarter turns $F(4)=2.82$, $p<0.05$ or photocell counts $F(4)=4.15$, $p<0.01$. However, there is evidence that the time of peak behavioral effect for haloperidol is not until at least 1 hr post-injection [36]. If only the final 30 min of the rotation test of this experiment are analyzed, 1 way analysis of variance indicates an overall significant inhibitory effect of haloperidol on net rotation $F(4)=3.16$, $p<0.05$ and net rotation is significantly depressed by 1, 2 and 4 mg/kg ($p<0.05$, Duncan's Multiple Range test). The time lag in the effect of haloperidol may explain why haloperidol had a significant effect on photocell counts since this measure was actually recorded 60 min post-injection.

AMPT produced no significant effects on rotation. Although AMPT increased extra quarter turns $F(3)=2.91$, $p<0.05$, no changes were observed in the photocell boxes $F(3)=0.19$, $p=0.90$. It is unlikely that the lack of effect of AMPT is simply attributable to the time course of the drug since neurochemical studies indicated that 75 mg/kg AMPT produces a significant depletion in cerebral dopamine and norepinephrine within 2 hr after administration [38].

The effects of these 4 drugs on seizure magnitude and

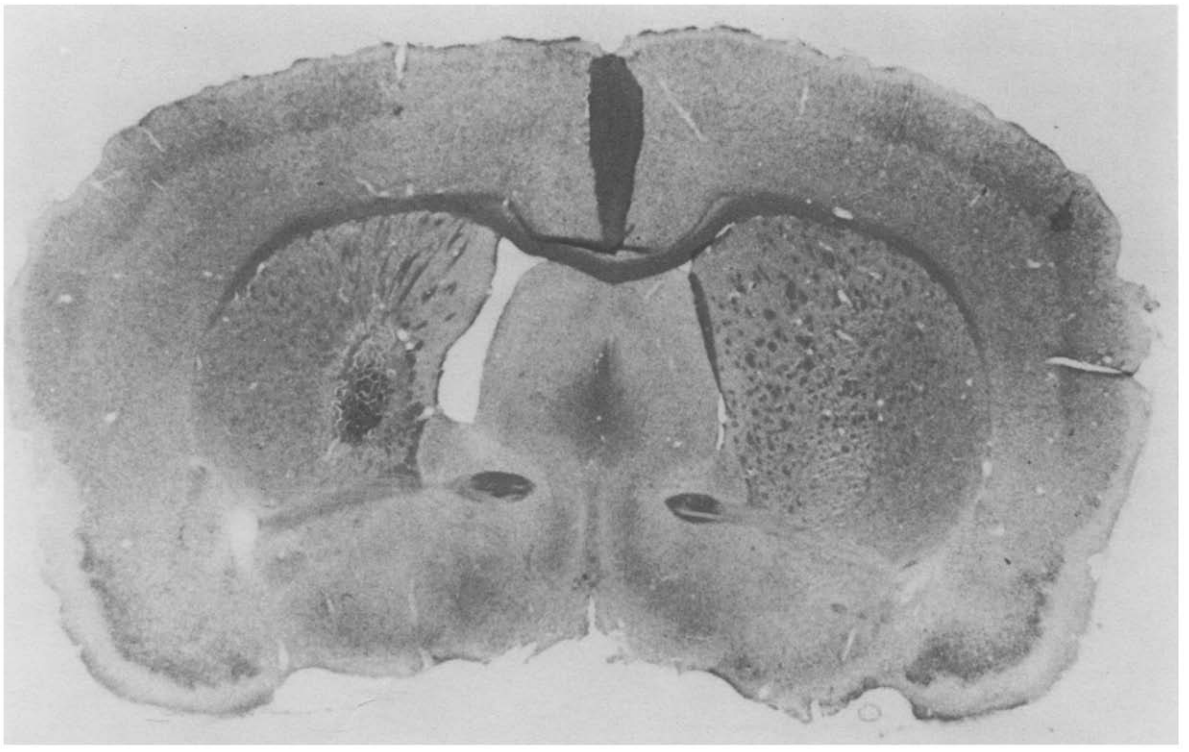

FIG 2. Representative brain section with unilateral neostriatal electrolytic lesion

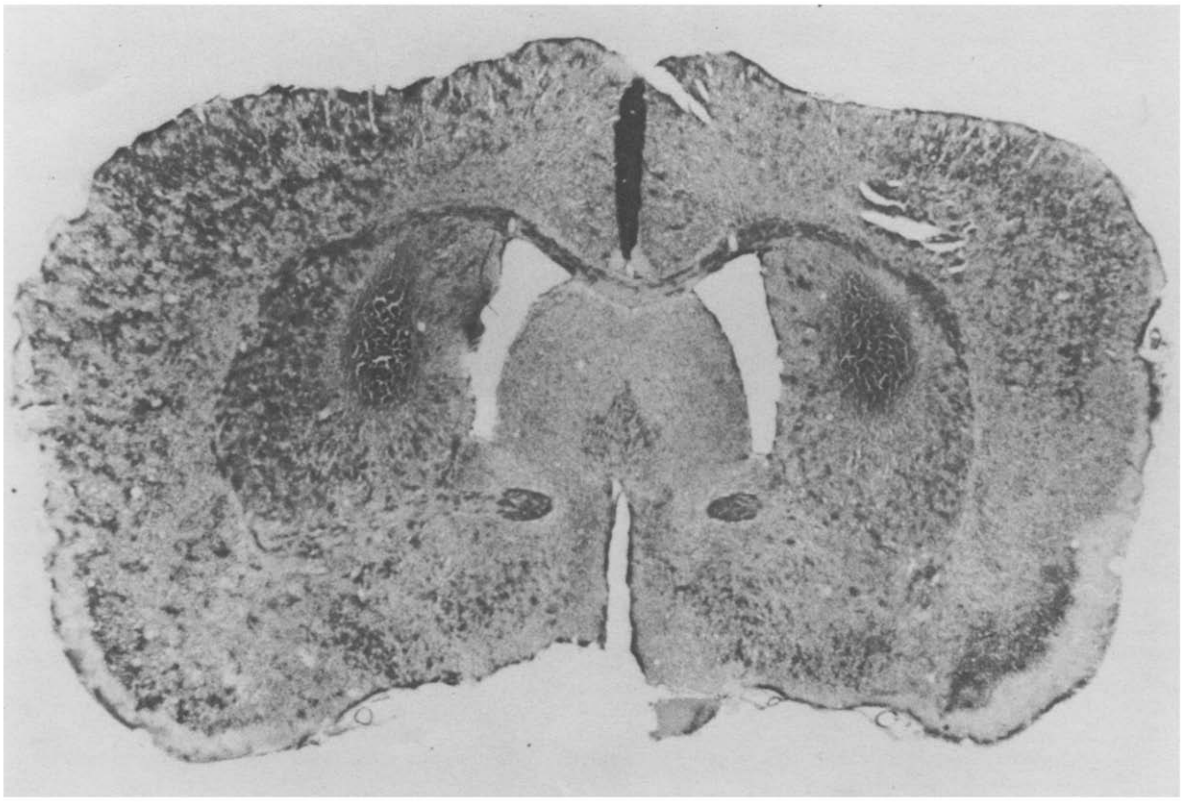

FIG 3. Representative brain section with bilateral neostriatal electrolytic lesion

TABLE 4
THE EFFECT OF STRIATAL LESIONS ON SEIZURE BEHAVIOR

| Sham Lesions | | Unilateral Lesions | | Bilateral Lesions | |
|---|---|---|---|---|---|
| Subject | Seizure Score* | Subject | Seizure Score* | Subject | Seizure Score* |
| 1 | −2 | 1 | −2 | 1 | 0 |
| 2 | +1 | 2 | −2 | 2 | +1 |
| 3 | +2 | 3 | +1 | 3 | +1 |
| 4 | +1 | 4 | −1 | 4 | −1 |
| 5 | 0 | 5 | −2 | 5 | +1 |
| 6 | +1 | 6 | −2 | 6 | 0 |
| 7 | +2 | 7 | +1 | 7 | +1 |
| 8 | −1 | 8 | +1 | 8 | +1 |
| 9 | 0 | 9 | +1 | 9 | −1 |
| | | 10 | −4 | 10 | +2 |
| | | 11 | +1 | 11 | +2 |
| | | 12 | −2 | 12 | +3 |
| | | 13 | −2 | 13 | −2 |
| | | 14 | −2 | 14 | −2 |
| | | 15 | −2 | 15 | 0 |
| | | 16 | +2 | 16 | −2 |
| | | 17 | +1 | 17 | −2 |
| | | 18 | −2 | | |
| | | 19 | +1 | | |
| | | 20 | −5 | | |
| | | 21 | −5 | | |
| | | 22 | −3 | | |
| | | 23 | +1 | | |
| | | 24 | +1 | | |

*Seizure Score: postoperative seizure score − preoperative seizure score.

frequency in gerbils are indicated in the last columns of Table 3. At 4 mg/kg, amphetamine reduced seizure severity ($p<0.05$, Chi-square test), this dose was the only one which increased dominance as well as net rotation. Apomorphine inhibited both the magnitude ($p<0.05$) and frequency ($p<0.001$, Chi-square tests) of seizures at 16 mg/kg, which was the only dose to increase both dominance and net rotation. In contrast, at 1 mg/kg haloperidol exacerbated seizure severity ($p<0.01$, Chi-square test) and reduced dominance significantly. At the doses tested, AMPT did not affect seizure activity or rotation.

## EXPERIMENT 3

### METHOD

In part 3 of the study, the effect of unilateral and bilateral neostriatal lesions on handling-induced seizure activity was determined. For this, subjects were first seizure tested in the morning and operated upon in the afternoon. All surgery was conducted under methoxyflurane inhalation anesthesia. Lesions were made with unipolar electrodes in the neostriatum by a direct anodal current of 1 mA for 5 sec. Stereotaxic coordinates [30] were 0.8 mm anterior to bregma, 2.8 mm lateral to the midline and 3.8 mm from the dorsal brain surface. Sham-operated controls had burr holes placed in the skull but did not undergo electrode placement. Unilateral lesions were placed in either left or right striatum.

After a 2 week recovery period, gerbils were again seizure tested. Subsequently, all gerbils were killed and perfused with 0.85% saline solution and followed by perfusion with 10% Formalin. The brains were removed and immersed in Formalin for at least a week before sections (40 $\mu$m stained with Luxol blue and cresyl violet) were made and histological examination was conducted.

### RESULTS

All lesions produced damage to a portion of the neostriatum. The caudate nucleus was most extensively involved although some lesions were located in the globus pallidus. A representative unilateral lesion is shown in Fig. 2. Bilateral lesions were not always symmetrical in size, location or rostrocaudal extent. The asymmetries, however, were small (Fig. 3).

None of the lesion or control groups had any effect on seizure frequency. Unilateral neostriatal lesions, however, significantly reduced seizure magnitude ($p<0.05$, Wilcoxon Signed Ranks test). There was no difference in seizure activity between subjects receiving left or right lesions. Bilateral neostriatal lesions and sham lesions had no effect on seizure severity ($p<0.05$, Wilcoxon Signed Ranks tests) (Table 4).

## DISCUSSION

Previous observations from this laboratory have shown that cerebral asymmetry in rodents modulates learning of both spatial and nonspatial tasks [13]. The results of the

present study suggest that cerebral asymmetry, as measured by rotational activity, influences sensory-induced seizure activity in gerbils.

## EXPERIMENT 1

The results of Experiment 1 showed that seizure sensitive gerbils make proportionally fewer rotations to a preferred direction than resistant animals. Differences between groups cannot be attributed simply to postictal effects since animals seized prior to Test 1 only and the greatest differences between groups was observed during Test 2 (data not presented). It is unlikely that the effects of the Day 1 seizure can last for 4 days, until Test 3, since the EEG of a nonconvulsing seizure sensitive gerbil generally shows no sign of paroxysmal activity [27]. In addition, learning deficits produced by seizure activity disappear within 24 hours [43]. However, the neurological changes associated with the postictal refractory period of 2–5 days after a major seizure in the gerbil [28] may underlie the observed results.

## EXPERIMENT 2

### *Anticonvulsant Drugs*

In Experiment 2A, the effects of 7 standard anticonvulsant drugs on rotation and activity in naive gerbils were evaluated. Five of these agents (carbamazepine, diazepam, pentobarbital, phenobarbital and ethosuximide) potentiated rotation while diphenylhydantoin and trimethadione were ineffective.

Different neurochemical mechanisms may underlie the observed effects on rotation of these drugs. For instance, carbamazepine, which structurally resembles the tricyclic antidepressants, has an antidepressant, "psychotropic" effect clinically [6] which suggests a dopaminergic stimulatory effect. In addition, the anticonvulsant effect of carbamazepine on electrically-induced seizures in rats can be antagonized by intraventricular 6-hydroxydopamine lesions [39] which indicates that the anticonvulsant effect is specifically mediated by dopaminergic mechanisms. In contrast, the lack of effect of diphenylhydantoin on rotation may be attributed to its possible dopaminergic antagonist properties. For instance, diphenylhydantoin decreases the therapeutic response to L-DOPA in Parkinson patients [31]. In the laboratory, diphenylhydantoin antagonizes L-DOPA [31], amphetamine and apomorphine induced [9] rotation in rodents with unilateral nigrostriatal lesions. These reports stand in contrast to reports in vitro that diphenylhydantoin stimulates catecholamine release [37], inhibits monoamine oxidase [3] and inhibits catecholamine reuptake [17].

In general, little is known about the effect of the barbiturates on catecholamines in the brain. In vitro, pentobarbital decreases norepinephrine uptake [26,49]. In behavioral studies, pentobarbital and barbital antagonized drug-induced rotation in rats with unilateral nigrostriatal lesions [2,46]. The rotation-enhancing effects of the barbiturates observed in this study may be related to stimulation of GABAergic neuronal systems [4, 35, 40, 49]. Several studies in rats have demonstrated that GABA and GABAergic drugs may modulate rotational behavior [8]; this effect is attributed to the effect of GABAergic striatonigral neurons on dopaminergic nigrostriatal neurons It is likely, too, that the increased rotation produced by diazepam, like its anticonvulsant action, is attributable to its GABA-stimulating effect.

To date, the neurochemical action of ethosuximide has not been elucidated. Pharmacological studies of pentylenetetrazol-induced seizures in mice suggest that serotonin, not the catecholamines, may mediate the anticonvulsant effect of ethosuximide [32] The effect, if any, of trimethadione on the catecholamines has not been determined.

### *Dopaminergic Drugs*

The results of Experiment 2B, which confirm and extend the original observations of Jerussi and Glick [20], indicate that agents which mimic the effect of dopamine, such as amphetamine and apomorphine, induce rotation while a drug which antagonizes dopaminergic activity, haloperidol, blocks rotation in intact gerbils.

Amphetamine-induced net rotation increased monotonically at low doses (0.5–4.0 mg/kg) until it reached an asymptote at approximately 90 net rotations at the higher doses (4–16 mg/kg). This relationship is in contrast to the biphasic curve observed in the rat [18] although for both species, the maximal rotational response per hour is the same. As in the rat and mouse, amphetamine-induced rotation in intact gerbils is believed to reflect a differential release of dopamine between striata, either because one striatum intrinsically contains more dopamine or its transmitter pool is more susceptible to the releasing action of the drug [21]. In fact, intact gerbils manifest a 33% striatal dopamine asymmetry [20].

At 4 mg/kg, amphetamine enhanced both net and dominance without a concomitant rise in locomotor activity (only the number of extra quarter turns is temporally correlated with the rotation data). However, at higher doses of amphetamine, inspection of the activity data indicates that although the magnitude of net rotation continued to increase as activity increased, dominance began to decrease Glick and coworkers [14] proposed that amphetamine-induced rotation is the result of asymmetric striatal dopamine release while the locomotor stimulatory effect could be attributed to release of dopamine per se in both striata

Apomorphine produced significant increases in net rotation and dominance at only the highest dose tested, 16 mg/kg. In normal rats, apomorphine-induced rotation is attributed to an intrinsic postsynaptic asymmetry in the nigrostriatal system [19].

The neuroleptic haloperidol produced a dose-dependent inhibition of rotation and one dose, 1 mg/kg, reduced dominance. The findings agree with the known inhibitory effect of haloperidol on rotation in normal and unilaterally nigral lesioned [48] rats, as well as in normal gerbils [20].

Alpha-methyl-para-tyrosine, an inhibitor of tyrosine hydroxylase, had no significant effects on net rotation or dominance, although at 300 mg/kg AMPT net rotation was at a very low level (mean=5.67 net rotations/hr). It is possible that the lack of effect by AMPT can be attributed to dosage or time effects although, as indicated previously, neurochemical studies in mice show that 75 mg/kg AMPT produces a significant depletion in cerebral catecholamine levels within 2 hours [38]

## EXPERIMENT 3

Unilateral striatal lesions reduced seizure severity in gerbils. Since such lesions result in ipsilateral rotation in other rodents, the present observations support the notion of an inverse relationship between striatal asymmetry and seizure behavior. Bilateral striatal lesions had no effect on seizures; therefore, striatal damage per se does not alter seizure behavior. Furthermore, the results clearly indicate that the

epileptogenic focus is not located within the striata since the frequency of seizures is not affected. Rather, the asymmetry simply modulates seizure severity.

Other investigators have not differentiated between unilateral and bilateral lesions when measuring effects on seizures. Bilateral lesions of the caudate enhanced audiogenic seizures in rats [24], chemically induced seizures in the cat [33] and rat [25] and electrically induced seizures in the cat [7]. However, Kesner [24] failed to observe any effect of caudate lesions on electrically induced seizure frequency and Adler [1] reported no change in seizure threshold following bilateral lesions of the caudate, globus pallidus or substantia nigra. Differential effects of unilateral and bilateral caudate lesions on other behaviors in rodents [10,42] has been attributed to the surgically induced striatal asymmetry

*Cerebral Lateralization and Seizures*

Several observations presented in this report indicate an inverse relationship between rotation and seizure susceptibility: (1) Normal seizure resistant gerbils turn proportionally more to a preferred direction than sensitive gerbils in an hourly test session. (2) At least 3 antiepileptic drugs, phenobarbital, pentobarbital and ethosuximide, stimulate rotation at anticonvulsant doses. (3) Two dopaminergic agonists, amphetamine and apomorphine, have anticonvulsant activity at doses which enhance rotation while a dopaminergic antagonist, haloperidol, inhibits rotation and increases seizure severity. (4) Surgically induced asymmetry between the striata reduces seizure severity

One hypothesis which may explain how cerebral asymmetry modifies seizure activity is based on the idea that an optimal degree of nigrostriatal asymmetry underlies the orientation response of an animal to novelty [15]. Since the effectiveness of a seizure-initiating stimulus is directly related to its stress-inducing properties [23], an orientation deficit would enhance seizure susceptibility by rendering the animal more prone to a startle reaction in response to a novel stimulus. Enhancement of the asymmetry by pharmacological or surgical means may facilitate orientation. In the normal gerbil, novel and stressful situations potentiate cerebral asymmetry [45].

It is difficult at this time to reconcile our conclusion that seizure activity and cerebral asymmetry are inversely related with that of Myslobodsky and Rosen [34] who found that chemically induced seizures produced rotation. For instance, if a unilateral deficit interfered with the inhibitory effect of the striatum on the thalamus and/or cortex and, thus, promoted the development of hypersynchronous electrical activity, as suggested by Msylobodsky and Rosen, one would have expected seizure sensitive gerbils to rotate *more* than resistant animals, in contrast to the observed results. The present study differs from the Myslobodsky and Rosen study in both the species studied and method of seizure initiation. It is important to note that the chemical convulsant produced asymmetric spike-wave activity while sensory-induced seizures of the gerbil are characterized by bilaterally symmetrical spike and wave activity [27].

In summary, the results show that normal (i.e. nonlesioned and nondrugged) gerbils which are resistant to sensory-induced seizures rotate proportionally more to one direction than seizure sensitive animals. In pharmacological studies, some (but not all) prototypical anticonvulsant drugs potentiate rotation at their seizure-limiting doses while drugs with dopaminergic activity had opposite effects on seizures and rotation Surgically induced asymmetry between the neostriata reduced seizure activity in sensitive gerbils. These results suggest an inverse relationship exists between seizure susceptibility and rotation, an index of laterality, which may be mediated via an asymmetry between the dopaminergic nigrostriatal systems

## REFERENCES


1 Adler, M. W. Laboratory evaluation of antiepileptic drugs—The use of chronic lesions *Epilepsia* **10:** 263–280, 1969

2 Anden, N E., A. Dahlstrom, K Fuxe and K Larsson. Functional role of the nigro-neostriatal dopaminergic neurons *Acta pharmac tox* **24:** 263–274, 1966

3 Azzaro, A J., J A Gutrecht and D J Smith Effect of diphenylhydantoin on the uptake and catabolism of L-($^3$H)-norepinephrine in vitro in the rat cerebral cortex tissue *Biochem Pharmac* **22:** 2719–2729, 1973

4 Bowery, N G. Reversal of the action of GABA antagonists by barbiturates *Br J Pharmac* **58:** 456P–457P, 1976

5. Cox, B and P. Lomax Brain amines and spontaneous epileptic seizures in the Mongolian gerbil *Pharmac Biochem Behav* **4:** 263–267, 1976

6. Dalby, M A. Behavioral effects of carbamazepine. *Adv Neurol* **11:** 331–343, 1975.

7 Demetrescu, M , M. Demetrescu and G Iosit. The tonic control of cortical responsiveness by inhibitory and facilitatory diffuse influences *Electroenceph clin Neurophysiol* **18:** 1–24, 1965.

8 Dray, A., L J Fowler, N R. Oakley, M A. Simmonds and T Tanner. Comparison of circling behavior following unilateral inhibition of GABA transaminase or discrete electrolytic lesioning in the rat substantia nigra *Br J Pharmac* **55:** 288P, 1975

9 Elliott, P. N C., P. Jenner, D. Chadwick, E. Reynolds and C D. Marsden The effect of diphenylhydantoin on central catecholamine containing neuronal systems *J Pharm Pharmac* **29:** 41–43, 1977.

10. Glick, S. D. and R. D. Cox. Differential effects of unilateral and bilateral caudate lesions on side preferences and timing behavior in rats *J. comp. physiol. Psychol.* **90:** 528–535, 1976.

11 Glick, S D., T. P. Jerussi and L N Fleischer Turning in circles· The neuropharmacology of rotation *Life Sci* **18:** 889–896, 1976

12. Glick, S D , T P. Jerussi, D H Waters and J P Green Amphetamine-induced changes in striatal dopamine and acetylcholine levels and relationship to rotation in rats *Biochem Pharmac* **23:** 3223–3225, 1974.

13. Glick, S D , T. P Jerussi and B. Zimmerberg Behavioral and neurochemical correlates of nigrostriatal asymmetry in rats. In *Lateralization in the Nervous System*, edited by S. Harnad, R W Doty, L Goldstein, J Jaynes and G Krauthamer New York Academic Press, 1977, pp. 213–249

14. Glick, S D., B. Zimmerberg and S Greenstein. Individual differences among mice in normal and amphetamine-enhanced locomotor activity Relationship to behavioral indices of striatal asymmetry. *Brain Res.* **105:** 362–364, 1976.

15 Glick, S. D., B Zimmerberg and T. P Jerussi Adaptive significance of laterality in the rodent In *Evolution and Lateralization of the Brain*, edited by S. J Dimond and D A Blizard New York N.Y Academy Science, 1977, pp 180–185

16 Greenstein, S and S D. Glick Improved automated apparatus for recording rotation in rats and mice *Pharmac Biochem Behav* **3:** 507–510, 1975

17 Hadfield, M G Uptake and binding of catecholamines. *Archs Neurol Psychiat* **26:** 78–84, 1972.
18 Jerussi, T P. and S. D Glick. Amphetamine-induced rotation in rats without lesions. *Neuropharmacology* **13:** 283–286, 1974
19. Jerussi, T P and S. D Glick. Apomorphine-induced rotation in normal rats and interaction with unilateral caudate lesions. *Psychopharmacologia* **40:** 329–334, 1975.
20. Jerussi, T. P. and S D. Glick Spontaneous and drug-induced rotation in the Mongolian gerbil *Behav. Biol* **16:** 241–244, 1976.
21 Jerussi, T P and S. D. Glick. Drug-induced rotation in rats without lesions. Behavioral and neurochemical indices of a normal asymmetry in nigrostriatal function. *Psychopharmacology* **47:** 249–260, 1976
22. Jerussi, T. P., S D. Glick and C. L. Johnson Reciprocity of pre- and postsynaptic mechanisms involved in rotation as revealed by dopamine metabolism and adenylate cyclase stimulation. *Brain Res* **129:** 385–388, 1977.
23 Kaplan, H What triggers seizures in the gerbil, Meriones unguiculatus? *Life Sci* **17:** 693–698, 1975
24. Kesner, R. P. Subcortical mechanisms of audiogenic seizures *Expl Neurol.* **15:** 192–205, 1966.
25. Kirkby, R J. Effects of lesions of the caudate nucleus or frontal neocortex on drug-induced seizures in the rat *Physiol Psychol* **5:** 359–363, 1977
26 Lidbrink, P. and C O. Farnebo Uptake and release of noradrenaline in rat cerebral cortex in vitro *Neuropharmacology* **12:** 1087–1095, 1973
27 Loskota, W. J. and P Lomax. The Mongolian gerbil as a model for the study of the epilepsies. EEG records of seizures. *Electroenceph clin Neurophysiol.* **38:** 579–604, 1975
28 Loskota, W. J., P Lomax and S. T. Rich The gerbil as a model for the study of the epilepsies Seizure habituation and seizure patterns *Proc. west Pharmac Soc* **15:** 189–194, 1972.
29 Loskota, W. J., P Lomax and S T Rich. The gerbil as a model for the study of the epilepsies. *Epilepsia* **15:** 109–119, 1974
30 Loskota, W. J., P. Lomax and M. A Verity. *A Stereotaxic Atlas of the Mongolian Gerbil Brain* Ann Arbor U of Michigan Press, 1974.
31 Mendez, J. S., G C Cotzias, I Mena and P. S. Papavasiliou Diphenylhydantoin Blocking of L-DOPA effects *Archs Neurol Psychiat* **32:** 44–46, 1975
32 Meyer, H. and H. H. Frey. Dependence of anticonvulsant drug action on central monoamines. *Neuropharmacology* **12:** 939–947, 1973
33 Mullan, S , G Vailati, J. Karasick and M Mailis Thalamic lesions for the control of epilepsy. *Archs Neurol Psychiat* **16:** 277–285, 1967.
34 Myslobodsky, M. and J. Rosen Hemispheric asymmetry of pentamethylenetetrazol-induced wave-spike discharges and motor imbalance in rats *Epilepsia* **20:** 377–386, 1979
35. Nicoll, R. A , J. C. Eccles, T Oshima and F. Rubia Prolongation of hippocampal inhibitory postsynaptic potentials by barbiturates *Nature* **258:** 625–627, 1975
36. Ohman, R , M. Larsson, I M. Nilsson, J Engel and A Carlsson Neurometabolic and behavioral effects of haloperidol in relation to drug levels in serum and brain *Archs Pharmac* **299:** 105–114, 1977
37. Pincus, J H and S. H. Lee. Diphenylhydantoin and calcium Relation to norepinephrine release from brain slices *Archs Neurol Psychiat* **29:** 239–244, 1973
38. Porter, C C , J. A Totaro, A Burcin and E R Wynosky The effect of the optical isomers of alpha-methyl-p-tyrosine upon brain and heart catecholamines in the mouse. *Biochem Pharmac.* **15:** 583–590, 1966
39. Quattrone, A. and R. Samanin Decreased anticonvulsant activity of carbamazepine in 6-hydroxydopamine-treated rats *Eur J Pharmac.* **41:** 333–336, 1977.
40 Raabe, W and R J Gumnit Anticonvulsant action of diazepam Increase of cortical postsynaptic inhibition *Epilepsia* **18:** 117–120, 1977
41 Ransom, B R and J L. Barker Pentobarbital modulates transmitter effects on mouse spinal neurones grown in tissue culture. *Nature* **254:** 703–705, 1975
42 Rothman, A. H and S D Glick. Differential effects of unilateral and bilateral caudate lesions on side preference and passive avoidance behavior in rats *Brain Res* **118:** 361–369, 1976
43 Schonfeld, A. R. and S D Glick Effect of handling-induced seizures on passive avoidance behavior in gerbils *Behav Biol* **24:** 101–106, 1978.
44 Schonfeld, A R. and S D Glick Neuropharmacological analysis of handling-induced seizures in gerbils *Neuropharmacology* **19:** 1009–1016, 1980.
45. Schonfeld, A R and S D Glick Circadian studies of the spontaneous rotational behavior of the gerbil. *Physiol Behav* **25:** 337–340, 1980
46. Slater, P Effect of tolerance to morphine, ethanol and barbiturate on amphetamine circling in rats with a striatal dopamine lesion. *J Pharm Pharmac* **30:** 88–91, 1978.
47 Thiessen, D D , G Lindzey and H D Friend Spontaneous seizures in the Mongolian gerbil. *Psychon Sci* **11:** 227–228, 1968
48. Ungerstedt, U Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior *Acta Physiol. Scand Suppl* **367:** 49–68, 1971.
49 Weinberger, J., W. J. Nicklas and S Berl Mechanism of action of anticonvulsants *Neurology* **26:** 162–166, 1976