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Seizure Promotion and Protection by D-1 and D-2 Dopaminergic Drugs in the Mouse

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BURKE, K., C. J. CHANDLER, B. S. STARR AND M. S. STARR. *Seizure promotion and protection by D-1 and D-2 dopaminergic drugs in the mouse*. PHARMACOL BIOCHEM BEHAV 36(4) 729–733, 1990.—Mice injected with pilocarpine (100–400 mg/kg plus 1 mg/kg methylscopolamine), picrotoxin (0.75–6 mg/kg) or strychnine (0.75–6 mg/kg) exhibited clonic or clonic/tonic convulsions. Pretreatment with the D-1 agonist CY 208–243 (0.375–1.5 mg/kg) dose-dependently potentiated the convulsions elicited by 100 mg/kg pilocarpine, but had neither a convulsant nor anticonvulsant effect in mice receiving picrotoxin (3 or 6 mg/kg) or strychnine (0.75 or 1.5 mg/kg). This facilitatory effect of CY 208–243 was abolished by the D-1 antagonist SCH 23390 (0.2 mg/kg). SCH 23390 by itself (0.05–0.8 mg/kg) dose-dependently protected mice against pilocarpine (400 mg/kg) seizures. Stimulating D-2 receptors with LY 171555 (0.167–4.5 mg/kg) dose-dependently protected mice against seizure activity induced by pilocarpine, but neither protected nor sensitised mice given picrotoxin or strychnine. The neuroleptics haloperidol (1–4 mg/kg), sulpiride (10–50 mg/kg), metoclopramide (1.25–6.25 mg/kg), thioridazine (0.5–2 mg/kg) and clozapine (0.5–2 mg/kg) had no effect on the seizure threshold to 100 mg/kg pilocarpine by themselves, although 10 mg/kg thioridazine and clozapine caused 100% convulsions, possibly through a toxic action. When administered in conjunction with a minimally effective quantity of CY 208–243 (0.375 mg/kg), however, all five neuroleptics interacted synergistically with the D-1 agonist to promote convulsions to pilocarpine (100 mg/kg). No such interaction occurred between submaximally protective doses of the D-1 blocker SCH 23390 (0.05 and 0.2 mg/kg) and a wide range of doses of the D-2 stimulant LY 171555 (0.167–4.5 mg/kg). It is concluded that in the pilocarpine-treated mouse, D-1 stimulation aggravates and D-1 blockade ameliorates seizure expression, while D-2 stimulation and blockade have exactly the opposite effect. The synergism between D-1 activation and D-2 antagonism suggests the two receptors operate independently of each other to modulate the propagation of limbic motor seizures evoked by pilocarpine.

Epilepsy Mouse Pilocarpine Picrotoxin Strychnine D-1 receptors D-2 receptors

EVIDENCE has accumulated over the past 15 years which points unmistakably to dopamine being a regulator of epileptiform activity in the brain (1–4, 8, 10, 13, 15, 18, 23, 25). Precisely how and where dopamine acts to control the spread of seizures is still only poorly understood, but new work is beginning to provide us with some fascinating insights, particularly with respect to defining an important role for the D-1 receptor (1–3, 5, 13, 21, 23, 25).

A recent report by Barone *et al.* (5), together with original data from our own laboratory (1–3, 21), have introduced the concept that dopamine may influence the expression of some motor seizures bidirectionally, depending on the balance of its activity at D-1 and D-2 receptors across the brain. Clearly, not all models of epilepsy involve neuronal circuitry that is amenable to manipulation by dopaminergic drugs (6, 13, 16), but the pilocarpine model of limbic seizures is one that responds to such treatment (1–3, 5, 23, 24).

Accordingly, it has been shown that agonists which engage central D-1 receptors, like SKF 38393 (19), lower the seizure threshold to pilocarpine (1–3, 5). On the other hand, inhibiting D-1 activity with the selective D-1 antagonist SCH 23390 (11) reduces the convulsant efficacy of pilocarpine, which implies there is an underlying D-1 dopaminergic tone somewhere in the brain, acting to facilitate the expression of motor seizures (1–3, 5). These findings complement the more traditionally held view of dopamine's anticonvulsant action at D-2 receptors [see (23)].

As to the anatomical location of the D-1 and D-2 receptors mediating the pro- and anticonvulsant effects of dopaminergic agents, the nigrostriatal dopamine axis is emerging as a prime suspect. Turski *et al.* (23) discovered that D-2 agonists protected rats against pilocarpine-induced electrographic seizures and convulsions, when the compounds were microinjected stereotaxically into the dopamine-rich terminal fields of the anterior striatum. Subsequently, we showed that the forepaw myoclonus, rearing and falling, all of which are characteristic features of systemic treatment with SKF 38393 and a threshold convulsant dose of pilocarpine, could be reproduced in their entirety by depositing the SKF 38393 into the substantia nigra pars reticulata (2,3). Similarly, the response to convulsant doses of pilocarpine could be allayed by injecting SCH 23390 directly into this nucleus (2,3). Taken together, these observations present us with the intriguing

possibility that dopamine, liberated endogenously from opposite ends of the same nigrostriatal neurone, has the opportunity either to increase or decrease seizure susceptibility, depending on which of its actions at nigral D-1 and striatal D-2 receptors prevails.

To test the generality of this statement, and its applicability to other seizure models, we have investigated how the convulsant potencies of pilocarpine, picrotoxin and strychnine in mice are modified by a selection of agonists and antagonists of D-1 and D-2 receptors. By judicious application of combinations of dopaminergic drugs, we have also attempted to assess the intrinsic pro- and anticonvulsant strengths of endogenous dopamine. Our results confirm the bimodal influence of dopamine on the propagation of limbic seizures, and indicate that separate manipulations of D-1 and D-2 receptors can interact in a synergistic fashion to increase, but not decrease seizure severity. From these data it is tentatively suggested that endogenous dopamine's anticonvulsant tendency at D-2 receptors outweighs any proconvulsant effect it may have at D-1 receptors.

METHOD

Behavioural Testing

Wistar albino mice (Olac), of either sex and weighing 20–35 g, were used in this study. Animals were housed in groups of twenty, at 22 ± 1°C, under fluorescent lighting from 0700–1700 hr and allowed free access to food and water.

Animals were placed in an open field (0.87 m diameter and 0.37 m high) and allowed to habituate to their new surroundings for 1 hr. They were then injected with vehicle (controls) or test dopaminergic drug and returned to the open field. Subsequently, they received one of a range of doses of pilocarpine, picrotoxin or strychnine and observed for overt signs of seizure activity over the following 4 hr. Methylscopolamine, 1 mg/kg, was always administered prior to pilocarpine to inhibit the peripheral autonomic effects of the cholinomimetic.

Seizure frequencies were compared by Fisher Exact Probability test.

Drugs

All drugs were dissolved in demineralised water and injected in a volume of 5 ml/kg. Drug sources, pretreatment times (where appropriate) and routes of injection were as follows: pilocarpine nitrate (Sigma, IP); (−)-scopolamine methylbromide (Sigma, 30 min, IP); picrotoxin (Sigma, IP); strychnine hydrochloride (Sigma, IP); SKF 38393 (Research Biochemicals, 30 min, IP); CY 208–243 (Sandoz, 60 min, IP); LY 171555 (Lilly, 30 min, SC); apomorphine hydrochloride (Sigma, 30 min, SC); SCH 23390 (Schering, 60 min, IP); haloperidol (Sigma, 60 min, IP); sulpiride (Chemitechna Ltd., 60 min, IP); metoclopramide (Beechams, 60 min, IP); thioridazine (Sandoz, 60 min, IP); clozapine (Sandoz, 60 min, IP). CY 208–243, haloperidol and sulpiride were dissolved with the aid of one drop glacial acetic acid.

RESULTS

Control experiments were first conducted in order to establish the convulsant potencies of the cholinomimetic pilocarpine, the chloride channel blocker picrotoxin and the glycine receptor antagonist strychnine, under the conditions of this study. Results are illustrated in Table 1. All three compounds induced clonic or clonic/tonic convulsions with latencies and severities related to the dose. From these data, threshold and fully convulsant dose levels were selected for each compound, against which the potential pro- and anticonvulsant activities of dopaminergic agents would subsequently be screened. These were 100 and 400 mg/kg pilocarpine, 3 and 6 mg/kg picrotoxin, 0.75 and 1.5 mg/kg strychnine.

TABLE 1

RELATIVE POTENCIES OF THREE DIFFERENT CONVULSANTS IN MICE

Treatment	Dose (mg/kg)	% Convulsing	% Fatalities
Vehicle	—	0	0
Pilocarpine	100	5.0	0
	200	28.6	0
	400	90.9*	18.2
Picrotoxin	0.75	0	0
	1.5	0	0
	3	16.7	0
	6	100*	0
Strychnine	0.75	0	0
	1.5	87.5*	50
	3	100*	100*
	6	100*	100*

All drugs were injected intraperitoneally (IP) in water. Mice receiving pilocarpine were pretreated with 1 mg/kg IP methylscopolamine, 30 min beforehand. All mice were observed for a period of 4 hr. *$p<0.005$ versus vehicle by Fisher Exact test (n = 6–20).

When administered alone across the dose range 0.375–1.5 mg/kg, the D-1 agonist CY 208–243 elicited pronounced whole body grooming, sniffing and locomotion, as noted previously (7), but never caused the mice to convulse. However, CY 208–243 potently facilitated the convulsant action of a threshold amount of pilocarpine (100 mg/kg) in a dose-dependent manner (Table 2). This proconvulsant effect of CY 208–243 was prevented completely by pretreating the mice with the selective D-1 antagonist, SCH 23390 (0.2 mg/kg).

To determine whether SCH 23390 had an anticonvulsant action of its own, the benzazepine was administered to mice in combination with a convulsant dose of pilocarpine (400 mg/kg). It will be seen from Table 3 that D-1 blockade significantly lowered the seizure severity of central cholinergic stimulation, but only at high doses of SCH 23390.

Previous work has demonstrated that the acute antagonism of D-2 receptors by neuroleptics is also capable of promoting seizure activity, though this usually requires high (and presumably unselective) doses of the D-2 blockers [e.g., (23)]. In the present

TABLE 2

D-1 RECEPTOR-MEDIATED PROCONVULSANT EFFECT OF CY 208–243 IN PILOCARPINE-TREATED MICE

Treatment	Dose (mg/kg)	% Convulsing to 100 mg/kg Pilocarpine	
		(−)-SCH 23390	(+)-SCH 23390
Vehicle	—	5.0	0
CY 208–243	0.375	21.4	0
	0.75	83.3	0*
	1.5	100	0†

SCH 23390 (0.2 mg/kg) was injected 60 min, while methylscopolamine (1 mg/kg all animals) and CY 208–243 were injected 30 min before pilocarpine. All drugs were delivered intraperitoneally. *$p<0.05$, †$p<0.005$ versus CY 208–243 alone by Fisher Exact test (n = 6–20).

TABLE 3

ANTICONVULSANT EFFECT OF SCH 23390 IN PILOCARPINE-TREATED MICE

Treatment	Dose (mg/kg)	Response to 400 mg/kg Pilocarpine % Convulsing	% Fatalities
Vehicle	—	90.9	18.2
SCH 23390	0.05	100	14.3
	0.1	42.9*	0
	0.2	42.9*	0
	0.8	14.3†	0

SCH 23390 was injected 60 min and methylscopolamine (1 mg/kg all animals) 30 min prior to pilocarpine. All drugs were delivered IP. *$p<0.05$, †$p<0.005$ versus vehicle by Fisher Exact test (n = 7–11).

study, we found that haloperidol, sulpiride, metoclopramide, thioridazine and clozapine, administered systemically in doses that would normally be expected to block central D-2 receptors, had no effect on the animals' convulsant sensitivity to pilocarpine (Table 4). At 10 mg/kg, however, thioridazine and clozapine evoked 100% convulsions in mice treated with 100 mg/kg pilocarpine.

Interestingly, when CY 208–243 (0.375 mg/kg) was delivered in conjunction with otherwise ineffective doses of each of the five neuroleptics, plus a normally subconvulsant amount of pilocarpine (100 mg/kg), there was a pronounced synergism between the convulsant tendencies of D-1 stimulation and D-2 blockade (Table 4). Similar results were also obtained with SKF 38393 (30 mg/kg) and pilocarpine (100 mg/kg), which together caused 2/10 mice to convulse; this figure increased to 16/22 in the additional presence of metoclopramide (6.25 mg/kg, $p<0.05$).

The selective D-2 agonist, LY 171555 (0.167–4.5 mg/kg), had the opposite effect to CY 208–243 and protected mice against pilocarpine convulsions (Table 5). The anticonvulsant response to

TABLE 4

SYNERGISM BETWEEN THE CONVULSANT EFFECTS OF NEUROLEPTICS AND CY 208-243 IN PILOCARPINE-TREATED RATS

Neuroleptic	Dose (mg/kg)	% Convulsing to 100 mg/kg Pilocarpine (−)-CY 208–243	(+)-CY 208–243
Vehicle	—	5.0	21.4
Haloperidol	1	0	75.0*
	4	0	100†
Sulpiride	10	0	50.0
	50	0	75.0*
Metoclopramide	1.25	0	75.0*
	6.25	0	100†
Thioridazine	0.5	0	75.0*
	2	0	100†
	10	100	100
Clozapine	0.5	0	37.5
	2	0	75.0*
	10	100	100

All neuroleptics were injected 60 min and methylscopolamine (1 mg/kg all animals) 30 min before pilocarpine. All drugs were delivered IP *$p<0.05$, †$p<0.01$ versus neuroleptic or CY 208–243 alone by Fisher Exact test (n = 6–14).

TABLE 5

LACK OF SYNERGISM BETWEEN THE ANTICONVULSANT EFFECTS OF D-2 STIMULATION AND D-1 BLOCKADE IN PILOCARPINE-TREATED MICE

Treatment	Dose (mg/kg)	% Convulsing to 400 mg/kg Pilocarpine (−)-SCH 23390	(+)-SCH 23390 0.05 mg/kg	0.2 mg/kg
Vehicle	—	90.9	100	42.8
LY 171555	0.167	75.0	75.0	62.5
	0.5	50.0	50.0	50.0
	1.5	50.0	75.0	37.5
	4.5	0*	0*	0*

SCH 23390 was injected 60 min, methylscopolamine (1 mg/kg all animals) and LY 171555 30 min before pilocarpine. LY 171555 was injected subcutaneously, the rest intraperitoneally. *$p<0.005$ versus vehicle by Fisher Exact test (n = 6–11).

4.5 mg/kg LY 171555 was abolished by pretreatment with 0.25 mg/kg metoclopramide (0/8 convulsed, $p<0.005$). In these experiments, there was no evidence of a cooperative interaction between the anticonvulsant effects of LY 171555 (0.167–4.5 mg/kg) and those of SCH 23390 (0.05 and 0.2 mg/kg), since concomitant treatments with the two drugs afforded no greater protection than either compound injected alone (Table 5).

To determine if the selective D-1 and D-2 agonists were similarly efficacious in other mouse models of epilepsy, the experiments were repeated in mice administered threshold and fully convulsant doses of picrotoxin (Table 6) or strychnine (Table 7). In neither case were seizure frequencies increased or decreased by D-1 or D-2 stimulation. We also tested the mixed D-1/D-2 agonist, apomorphine (0.5–4.5 mg/kg), which allegedly augments strychnine-induced convulsions in the rat (18), but saw no indica-

TABLE 6

LACK OF CONVULSANT OR ANTICONVULSANT EFFECT OF SELECTIVE D-1 AND D-2 DOPAMINE RECEPTOR AGONISTS ON PICROTOXIN-INDUCED SEIZURES IN MICE

Treatment	Dose (mg/kg)	Picrotoxin (mg/kg)	% Convulsing
Vehicle	—	3	16.7
	—	6	100
CY 208–243	0.375	3	0
	0.75	3	0
	1.5	3	0
	0.375	6	100
	0.75	6	100
	1.5	6	100
LY 171555	0.5	3	0
	1.5	3	0
	4.5	3	0
	0.5	6	100
	1.5	6	100
	4.5	6	100

CY 208–243 (IP) and LY 171555 (SC) were injected 30 min prior to picrotoxin (IP). n = 6–10 mice per group. Animals were observed for 4 hr.

TABLE 7

LACK OF CONVULSANT OR ANTICONVULSANT EFFECT OF SELECTIVE D-1 AND D-2 DOPAMINE RECEPTOR AGONISTS ON SEIZURE ACTIVITY IN STRYCHNINE-TREATED MICE

Treatment	Dose (mg/kg)	Strychnine (mg/kg)	% Convulsing
Vehicle	—	0.75	0
	—	1.5	87.5
CY 208–243	0.375	0.75	0
	0.75	0.75	0
	1.5	0.75	0
	0.375	1.5	100
	0.75	1.5	100
	1.5	1.5	100
Apomorphine	0.5	0.75	0
	1.5	0.75	0
	4.5	0.75	0
LY 171555	0.5	0.75	0
	1.5	0.75	0
	4.5	0.75	0
	0.5	1.5	100
	1.5	1.5	100
	4.5	1.5	100

CY 208–243 (IP), apomorphine (SC) and LY 171555 (SC) were injected 30 min before strychnine (IP). n = 6–14 per group. Animals were observed for 4 hr.

tion of any such effect in the mouse (Table 7).

DISCUSSION

Recently, our own group (1–3, 21) and Barone *et al.* (5) have shown independently that SKF 38393 is proconvulsant, by virtue of its ability to activate D-1 receptors in the brain. Both studies made use of rats administered centrally active doses of the cholinergic agonist pilocarpine, since this compound induces convulsions that are said to parallel the human condition of secondarily generalised seizures, the commonest form of epilepsy in man (5, 23, 24). The present work confirms these findings with CY 208–243 in mice, and lends weight to the hypothesis that dopamine acts in two directions to control the motor expression of seizures in this model.

CY 208–243 is a drug recently introduced as a novel D-1 agonist, though it has unusual properties. In vitro it binds with high affinity to both D-1 and D-2 receptor binding sites (12,14), yet gives the appearance of only being active at D-1 receptors in vivo (7, 12, 14). We have found that the motor stimulant actions of CY 208–243, in habituated mice, are abolished by the D-1 blocking drug SCH 23390 (7), and the same is now true for CY 208–243's proconvulsant efficacy in pilocarpine-treated mice (see above). Thus, in spite of its unselectivity for D-1 and D-2 attachment points in mouse striatal homogenates (12), CY 208–243 nevertheless appears to be a valid pharmacological tool for investigating D-1 mechanisms in the whole animal.

In the present study, we have used motor manifestations as our sole criterion of epileptic activity. We would emphasise, however, that Barone *et al.* (5) found SKF 38393 not only produced florid motor symptoms, identical to those we saw with CY 208–243, but also gave rise to cortical and hippocampal electrographic changes, as well as extensive neuronal degeneration, which were typical of the convulsions elicited by higher doses of the cholinomimetic alone (23,24). It is interesting that both SKF 38393 and CY 208–243 promoted convulsions at dose levels that were approximately 10-fold lower than those normally required to induce hypermotility and grooming (5,7), as this suggests that two distinct subpopulations of D-1 receptors are engaged in these activities. A functional differentiation of D-1 receptors is highly likely, in fact, considering that the D-1 receptors concerned with locomotion and stereotypy have been localised to the nucleus accumbens (17) and striatum (20), whereas D-1 receptors in the substantia nigra have been implicated in the augmentation of motor seizures (2,3).

In the pilocarpine model of epilepsy, D-1 and D-2 receptors would also appear to be functionally and anatomically discrete. In contrast to the proconvulsant action of SKF 38393 in the nigra (2,3), the anticonvulsant effects of the D-2 agonist, LY 171555, are duplicated by intracerebral application of the drug into the anterior striatum (23). Since both of these brain regions are crucially concerned with both motor responding and seizure expression, these stereotaxic data collectively suggest that striatal D-2 and nigral D-1 receptors are strategically placed to regulate the motor signs of limbic seizures generated by pilocarpine (5,23), but do not participate in the initiation of epileptic discharges *per se*. This conclusion is in keeping with the detailed anatomic considerations of the pilocarpine model of epilepsy discussed by Turksi *et al.* (23).

There are many other animal models of epilepsy which either do not respond to dopaminergic drugs, or else do so in a way that is different from that described here (6, 13, 16, 18, 25). In some cases this is probably because the syndrome is outside the jurisdiction of the basal ganglia, while in others it can be traced to a difference between species. Strychnine convulsions, for instance, are considered to be primarily of bulbo-spinal origin. Nevertheless, they are allegedly abolished by MPTP in the mouse (9) and strengthened by apomorphine in the rat (18), implicating a caudally projecting dopamine system in their control. We had hoped to show if the facilitatory effect of apomorphine described by Sandoval and Palermo-Neto (18) was a D-1 receptor-mediated response, but in the event we found strychnine-treated mice were unresponsive to apomorphine, CY 208–243 and LY 171555 alike.

These same authors also showed that picrotoxin-induced seizures were enhanced by acute treatment with neuroleptics (18), yet our own study failed to disclose any effect of D-1 or D-2 stimulation on picrotoxin convulsions in mice. The reasons for these apparent disparities are not understood.

It is reasonable to assume that if the epileptic activity evoked by pilocarpine can be worsened by blocking D-2 receptors, and ameliorated by blocking D-1 receptors, then endogenous dopamine must be tonically active at both receptor sites during the course of the seizure. Microdialysis studies are in progress which, it is hoped, will reveal if this extracellular dopamine is present at normal physiological concentrations, or whether the release of dopamine is altered by the epileptic discharge. Turski *et al.* (23) reported that haloperidol (D-2>D-1 blocker) is proconvulsant, but only at doses that render the animals cataleptic, and which can no longer be considered to be selective for dopamine receptors. The butyrophenone was similarly ineffective in our hands, along with four other pharmacologically diverse neuroleptics—sulpiride, metoclopramide, thioridazine and clozapine. Admittedly the latter two compounds, at 10 mg/kg, caused mice to convulse in response to a subthreshold dose of pilocarpine, but this could be related to a toxic effect of the drugs rather than their capacities to occlude dopamine receptors.

Blocking D-2 receptors acutely, therefore, was clearly not sufficient to disclose a residual convulsant action of endogenous dopamine at D-1 receptors under the conditions of these experiments. It was noticeable, however, that when an additional D-1 stimulus in the form of a low dose of CY 208–243 was superim-

posed, there was a marked synergism between the D-1 agonist and each of the neuroleptics tested. These observations further indicate that we are dealing with D-1 and D-2 mechanisms that are discrete and work independently of each other, as otherwise the drug mixtures would not have elicited a greater than additive convulsant response.

Barone *et al.* (5) reported that SCH 23390 was potently anticonvulsant, whereas in our hands much larger quantities of the benzazepine were needed to demonstrate a beneficial effect (1). Interestingly, there was no equivalent synergistic interaction between the protective properties of SCH 23390 and LY 171555, administered in combination with a dose of pilocarpine that was sufficient to produce convulsions in 91% of animals. It is therefore concluded that the intrinsic activity of endogenous dopamine at D-1 receptors must be low, since the blockade of D-1 receptors contributes little to the more powerful anticonvulsant action of LY 171555 at D-2 receptors.

In summary, the pilocarpine-treated mouse appears to be a useful model for investigating the opposing roles of D-1 and D-2 receptors in the mechanisms governing the spread of seizures, while mice induced to convulse with picrotoxin or strychnine are less suited to this task. Acute stimulation of dopamine receptors is more efficient than acute blockade as a means of modifying seizure severity, suggesting any intrinsic control by endogenous dopamine is normally weak. On balance, it is suggested that dopamine's anticonvulsant activity (at D-2 receptors) probably outweighs its proconvulsant effects (at D-1 receptors), judging from the synergistic way in which combined D-2 blockade and D-1 stimulation are able to provoke convulsions.

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