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D-2 Agonists Protect Rodents Against Pilocarpine-Induced Convulsions by Stimulating D-2 Receptors in the Striatum, But Not in the Substantia Nigra

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AL-TAJIR, G. AND M. S. STARR. *D-2 agonists protect rodents against pilocarpine-induced convulsions by stimulating D-2 receptors in the striatum, but not in the substantia nigra.* PHARMACOL BIOCHEM BEHAV **39**(1) 109–113, 1991.—This study employed the pilocarpine model of epilepsy to determine the relative systemic anticonvulsant potencies of five different D-2 agonists in the mouse, and to investigate the site of anticonvulsant action of LY 171555 in the rat's brain following intracerebral microinjection. Control mice pretreated with saline developed motor seizures when challenged with pilocarpine (400 mg/kg, 11/13 convulsed). D-2 agonists protected mice against pilocarpine-induced seizures in the rank order of potency PHNO>pergolide>lisuride = LY 171555>>RU 24213, with ED_{50} values ranging from 0.17 mg/kg for PHNO to >4.5 mg/kg for RU 24213. The response to LY 171555 was abolished by the D-2 blocker metoclopramide (1.25 mg/kg), but not by the D-1 antagonist SCH 23390 (0.25 mg/kg). All D-2 agonists induced head-down sniffing and forward locomotion, consistent with central D-2 activation. LY 171555 (ED_{50} 0.19 mg/kg), but not RU 24213 (ED_{50}>4.5 mg/kg), was similarly efficacious in the rat. When injected into both hemispheres of the conscious rat via indwelling cannulae, intrastriatal saline failed to afford protection against the convulsant action of pilocarpine (600 mg/kg, 13/15 convulsed), whereas LY 171555 did (1 μg, 1/12 convulsed). Intrastriatal RU 24213 (1 μg per side) was without effect (7/10 convulsed). Similarly, no protection resulted when saline (15/16 convulsed) or LY 171555 (1 μg, 17/23 convulsed) were delivered into both nigras. It is concluded that in this model of limbic seizures in the mouse and rat, D-2 agonists exert a powerful anticonvulsant effect which is mediated by D-2 receptors in the striatum, but not by D-2 receptors in the substantia nigra.

Pilocarpine Convulsions D-2 agonists Corpus striatum Substantia nigra

CONSIDERABLE progress has been made in the past few years in unravelling the role of dopamine in the execution of motor seizures, with particular emphasis being laid on the dopamine-sensitive pilocarpine model of epilepsy. Systemic administration of a large dose of pilocarpine leads to excessive cholinergic stimulation in the brain, which in turn manifests itself as alterations in electroencephalographic activity, cell damage and intractable convulsions (8, 12, 40, 41). The attraction of this model is that dopamine can reliably modulate the development of the limbic seizure in two quite separate ways, via its opposite actions at D-1 and D-2 receptors (1, 3, 4, 8, 11, 38, 39).

It now looks as though the traditional anticonvulsant response to nonselective dopamine agonists, for example apomorphine (5, 27, 30), is mediated by the D-2 subclass of dopamine receptors, since compounds which preferentially activate the D-2 receptor, such as LY 171555 (37), are similarly beneficial (1, 3, 11, 38). Conversely, it has been shown that D-1 agonists, like the benzazepine SKF 38393 (32) and the newer phenanthridine derivative CY 208-243 (25), have the opposite effect to D-2 stimulants and increase the susceptibility of rats and mice to the convulsant actions of pilocarpine (1, 3, 4, 8, 39). We have suggested, therefore, that the physiological balance of dopamine's activity at its two different recognition sites within the brain is a major factor in determining whether the animal reacts favourably or adversely to seizure-promoting stimuli (1,4).

Autoradiographic mapping has revealed that D-1 and D-2 receptors are widely distributed across the brain, with highest densities occurring in the basal ganglia (13,31). Given the controlling influence that the basal ganglia have on the expression of seizures via the striatonigral connection (17), it is not surprising that the reciprocal nigrostriatal dopamine system has attracted attention as a likely site in the brain at which peripherally administered dopaminergic drugs act to produce their proconvulsant or anticonvulsant effects. As well as releasing their transmitter in the conventional manner from axon terminals, nigrostriatal dopamine neurones also have the capacity to liberate dopamine from dendritic branches in the substantia nigra (18), giving dopamine the opportunity of modulating the passage of information relevant to the production of motor seizures at either of these two anatomic sites.

One way of testing this hypothesis is to deliver dopaminergic drugs directly into the brain areas in question. Using the intracerebral microinjection approach, Turski et al. (38) delineated a D-2-dependent anticonvulsant site in the anterior part of the striatum. Similarly, we have shown that D-1 stimulants are proconvulsant

when applied to the substantia nigra (3,4), but not to the corpus striatum (2). However, blocking D-1 receptors in both of these areas, by focally injecting the selective D-1 antagonist SCH 23390 (20), successfully ameliorated pilocarpine-induced convulsions in both instances (2–4). One could argue, therefore, that D-1 receptors have a wider sphere of influence than D-2 receptors on the spread of pilocarpine-induced seizures, although a role of D-2 receptors at the level of the nigra cannot be ruled out.

The present study considers this point in more detail, by determining if LY 171555 is anticonvulsant when microinfused into the rat's substantia nigra. Also, because there is some confusion as to LY 171555's anticonvulsant efficacy by the systemic route (39), we have used the pilocarpine model of epilepsy to evaluate the seizure protection afforded by LY 171555 and several other D-2 agonists in the mouse. We shall present results which show that systemic D-2 agonists protect mice against limbic motor seizures with a rank order of potency that closely parallels their behavioural efficacies. As far as LY 171555 is concerned, this effect in the rat appears to derive solely from the activation of D-2 receptors at the striatal end of the nigrostriatal dopamine axis.

METHOD

Behavioural Testing

Wistar albino mice (20–35 g, Olac) and rats (150–200 g, Olac), of either sex, were used for these experiments. Mice were housed in groups of twenty rats in groups of ten, at 22 ± 1°C, under fluorescent lighting, between 0700–1700 h, and allowed free access to food and water. Behavioral testing was conducted between 1000–1700 h. All animals were used once only.

Animals were placed in groups of 5–15 in an open field (0.87 m diameter and 0.37 m high) and allowed to acclimatise for 1 h. They were then injected subcutaneously (SC) with saline (controls) or the D-2 agonist under test, together with methylscopolamine (1 mg/kg IP) to allay the peripheral effects of pilocarpine. In some experiments dopamine receptor antagonists were also administered IP at this stage and studied in parallel with controls. Thirty min later, a dose of pilocarpine, previously determined to be convulsant (1), was given to the mice (400 mg/kg IP) and rats (600 mg/kg IP). The frequency of motor seizures was then recorded over the next 4 h according to the behavioural criteria described by Turski et al. (38,40). A range of doses was tested for each D-2 agonist. The degree of protection (% controls) was plotted against log dose and ED_{50} values calculated as a measure of anticonvulsant potency. Individual results were compared by Fisher Exact Probability test.

Intracerebral Injections

Rats were fitted with bilateral stainless steel guide cannulae (external diameter 0.74 mm) as described earlier (4). The cannulae were positioned so as to lie 2–3 mm above the intended point of injection. One to two weeks later, bilateral treatments were made into the anterior striatum or substantia nigra, using an injection needle (external diameter 0.38 mm) connected to a 10 μl Hamilton syringe by narrow-bore polythene tubing. Dose volumes were 1 μl per striatum and 0.5 μl per nigra, expelled at a rate of 0.1 μl per 15 s. The injection needles were left in place for a further 1 min before being slowly withdrawn. The animals were injected concurrently with methylscopolamine (1 mg/kg IP) and 30 min later with pilocarpine (600 mg/kg IP). Seizure activity was then scored over a period of 4 h. Stereotaxic coordinates were A 1.0–2.8 mm from bregma, L 1.0–4.0 mm from midline, V 2.8–6.5 mm from brain surface for the corpus striatum, and A −4.8–5.0 mm from bregma, L 1.9–2.1 mm from midline, V 6.6–7.2 mm from brain surface for substantia nigra, according to the stereotaxic atlas of König and Klippel (23). At the end of each experiment the animals were sacrificed with sodium pentobarbitone (150 mg/kg IP, Expiral) and the brains removed for histological determination of injection sites as before (4).

TABLE 1

ANTICONVULSANT POTENCIES OF DOPAMINE D-2 RECEPTOR AGONISTS IN THE MOUSE AND RAT

D-2 Agonist	ED_{50} (mg/kg) Mouse	Rat
Lisuride	0.5	—
Pergolide	0.17	—
PHNO	0.07	—
LY 171555	0.5	0.19
RU 24213	>4.5	>4.5

Animals received one of a range of doses of D-2 agonist (SC) together with methylscopolamine (1 mg/kg IP), and challenged 30 min later with a convulsant dose of pilocarpine (400 mg/kg IP for mice, 600 mg/kg IP for rats). They were then observed for 4 h for signs of motor seizures and ED_{50} values calculated from log dose-response plots (n = 6–8 per dose).

Drugs

Drugs were either dissolved in demineralised water for systemic injection (5 ml/kg in mice, 1 ml/kg in rats), or in saline for intracerebral injection. Drug sources, pretreatment times (where appropriate) and routes of injection were as follows: pilocarpine nitrate (Sigma, IP); (−)-scopolamine methylbromide (Sigma, 30 min, IP); LY 171555 (Lilly, 30 min, SC); PHNO (Merck, 30 min, SC); RU 24213 (Roussel, 30 min, SC); lisuride hydrogen maleate (Schering, 30 min, SC); pergolide mesylate (Lilly, 30 min, SC); metoclopramide (Beechams, 30 min, IP); SCH 23390 (Schering, 30 min, IP).

RESULTS

In close agreement with earlier findings (1, 3, 11), pilocarpine, 400 mg/kg, induced motor convulsions in 11/13 saline-pretreated mice (Table 1). Prior to convulsing, the animals exhibited a variety of automatisms including tremor, teeth chattering and head scratching, followed by a characteristic sequence of head bobbing. The seizure itself consisted of rearing, myoclonic jerking of the forepaws (lasting 5–15 s) and loss of balance, with subsequent resumption of normal appearance. This sequence of behaviours steadily increased in frequency until they were virtually continuous and the mice were adjudged to be in status epilepticus (38,40). Three of the animals developed rapidly fatal tonic seizures.

Systemic pretreatment with D-2 agonists inhibited these pilocarpine-induced seizures in the following order of potency: PHNO>pergolide>lisuride = LY 171555>>RU 24213 (Table 1). RU 24213 gave no significant protection, even at 4.5 mg/kg (6/8 convulsed, $p>0.05$ versus controls). The anticonvulsant effect of LY 171555, 1.5 mg/kg, was prevented completely by the D-2-blocking drug metoclopramide (1.25 mg/kg, 6/6 convulsed, $p<0.05$), but not by the D-1 antagonist SCH 23390 (0.25 mg/kg, 0/6 convulsed, $p>0.05$).

A similar dissociation between the systemic anticonvulsant abilities of LY 171555 and RU 24213 was noted in the rat (Table 1). In both mice and rats, all of the D-2 agonists caused se-

TABLE 2

SEIZURE PROTECTION BY INTRASTRIATAL D-2 AGONISTS

Intrastriatal Treatment	Dose	Response to 600 mg/kg Pilocarpine Convulsions	Fatalities
Saline	1 μl	13/15	13/15
LY 171555	1 μg	1/12†	1/12†
RU 24213	1 μg	7/10	4/10*

Rats were equipped with bilateral stainless steel guide cannulae under halothane anaesthesia. One to two weeks later saline or D-2 agonist were delivered into both striata of conscious animals, and methylscopolamine (1 mg/kg IP) given to prevent the peripheral actions of pilocarpine. Thirty min later, pilocarpine (600 mg/kg IP) was administered and the incidence of seizure activity and mortality noted over the ensuing 4 h. *$p<0.05$, †$p<0.005$ versus saline by Fisher Exact Probability test.

dation in low doses, and prominent head-down sniffing and forward locomotion in high doses, consistent with the drugs entering the brain and stimulating D-2 receptors there.

Bilateral microinjections of saline delivered into the so-called "anticonvulsant region" of the anterior striatum (38), had no discernible effect on the sensitivity of rats to pilocarpine, 600 mg/kg (Table 2 and Fig. 1). On the other hand, LY 171555 (1 μg per side) significantly lowered the convulsion frequency and mortality rate from 86.7% to 8.3% ($p<0.005$ versus saline). Comparable injections of RU 24213 (1 μg per side) did not alter the frequency of convulsions, but reduced the number of deaths ($p<0.05$; Table 2 and Fig. 1).

The same dose of LY 171555 which was anticonvulsant in the striatum, failed to alter the course of pilocarpine-induced seizures from the substantia nigra (Table 3 and Fig. 2). The compound was ineffective both in the pars compacta and in the pars reticulata of this nucleus. We would point out, however, that the small fraction of rats not exhibiting motor seizures (6/23 animals) all

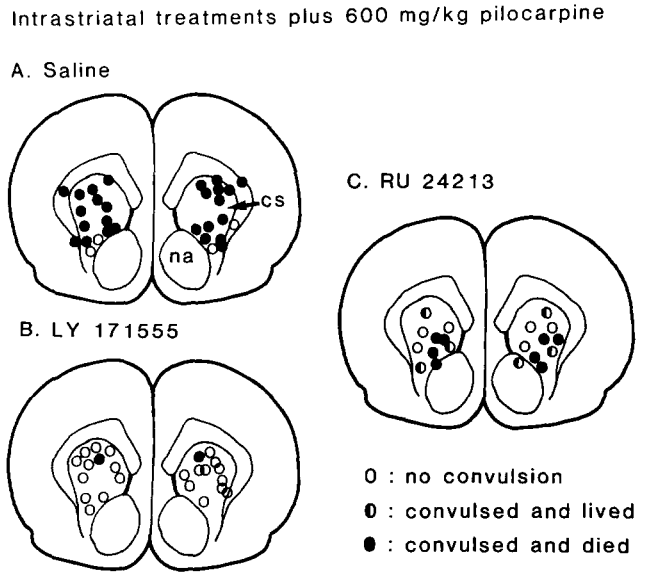

FIG. 1. Sites of anticonvulsant action of D-2 agonists injected bilaterally into the corpora striata of conscious rats. Details as for Table 2. na = nucleus accumbens; cs = corpus striatum.

TABLE 3

LACK OF SEIZURE PROTECTION BY INTRANIGRAL LY 171555

Intranigral Treatment	Dose	Response to 600 mg/kg Pilocarpine Convulsions	Fatalities
Saline	0.5 μl	14/15	10/15
LY 171555	1 μg	17/23	14/23

Details as for Table 2, except that all intracerebral injections were made in a volume of 0.5 μl.

received LY 171555 in the dorsolateral aspect of the pars reticulata, suggesting there may be a subdivision of the nigra capable of limiting seizure spread.

DISCUSSION

This study lends support to the notion that D-2 agonists are anticonvulsant, and that this beneficial effect derives from the stimulation of D-2 receptors in the striatum, as exemplified by the results we obtained with the potent and selective D-2 stimulant LY 171555 (37). By specifically targetting LY 171555 at the rostral striatum, using the stereotaxic approach, we can confirm what Turski et al. (38) have found previously, which is that seizure-inhibiting D-2 receptors are located discretely in the forebrain. In the present set of experiments, our sole criterion for seizure protection was whether the animal visibly convulsed or not. It is important to note, however, that the stimulation of D-2

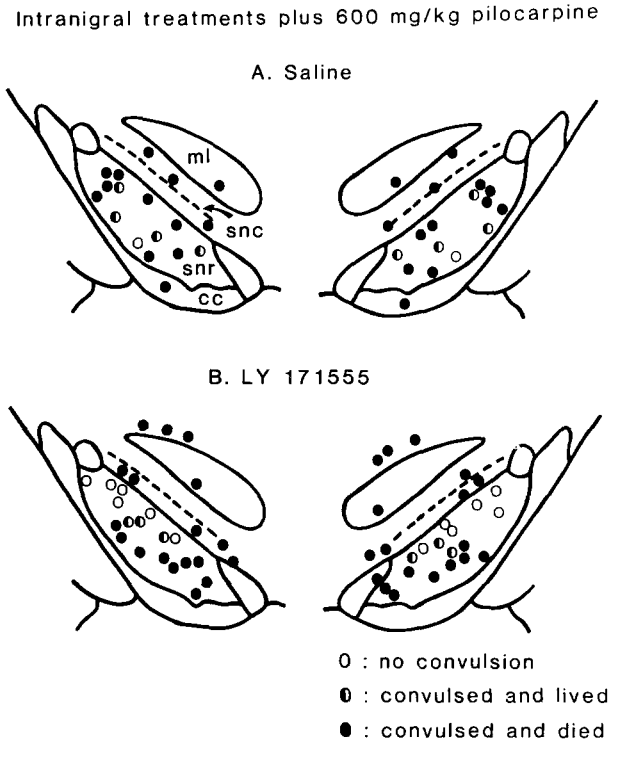

FIG. 2. Sites of injection of saline and LY 171555 in the substantia nigra of conscious rats which failed to modify pilocarpine-induced convulsions. Details as for Table 3. ml = medial lemniscus; cc = crus cerebri; snc = substantia nigra pars compacta; snr = substantia nigra pars reticulata.

receptors in the anterior striatum not only inhibits the motor expression of these limbic seizures, but also progressively normalises the high-voltage fast activity and spiking seen in the electroencephalogram, as well as preventing the acute neurotoxic damage (38, 40, 41).

On the other hand, LY 171555 had no clear-cut effect on the threshold to pilocarpine-induced motor seizures when the microinjections were restricted to either pars of the substantia nigra. From a purely statistical viewpoint, the frequency of convulsions for the intranigral LY 171555-treated group (74%) was not significantly different from the saline-treated controls (93%). All the same, it could be premature to dismiss entirely a protective role of nigral D-2 receptors in seizure mechanisms, since those rats which failed to convulse to pilocarpine (6/23) had all received LY 171555 in the dorsolateral aspect of the pars reticulata (Fig. 2). While this region is penetrated by dopaminergic dendrites from the pars compacta (22), we consider it unlikely that LY 171555 could have been anticonvulsant by depressing the excitability of dopamine cells, as there was no indication of any such effect when LY 171555 was deposited into the pars compacta itself. The D-2 agonist is in a position, however, to influence those reticulata neurones which are normally exposed to dopamine released from the closely apposed dopaminergic dendrites (18). Weick and Walters (44) have shown that iontophoretic LY 171555 reduces the firing rate of reticulata neurones, and since these in turn project to premotor nuclei outside the basal ganglia, a decrease in their firing rate would be entirely compatible with a seizure-limiting action of LY 171555 in this part of the brain (17,38). However, this proposal must remain speculative, until such time as a more elaborate topographic study confirms if there is indeed a discrete D-2-sensitive anticonvulsant subdivision of the substantia nigra, just as there is in the striatum (38).

A major and inexplicable discrepancy between our own work and that of Turski et al. (38) concerns the Polish workers' inability to protect rats with LY 171555 injected systemically (IP). We routinely administer D-2 agonists SC so as to reduce the likelihood of degradation by the abdominal route. Nevertheless, it seems unlikely that metabolic factors alone could account for the >150-fold difference in the anticonvulsant potency of LY 171555 between our two studies, especially when there is an abundance of data in the literature indicating that SC (6, 10, 33) and IP (7, 19, 21, 42) LY 171555 are equiactive in various behavioural tests.

Several other compounds with a proven pedigree of potent D-2 receptor stimulant activity were also quite capable of suppressing pilocarpine-induced convulsions, in keeping with this being a D-2 receptor-mediated response. Interestingly, the ratio of their potencies for the effect in the mouse (PHNO>pergolide>lisuride = LY 171555>>RU 24213) approximates closely to the relative abilities of these drugs to elicit contraversive asymmetries in the circling rat (PHNO>pergolide = lisuride>LY 171555>>RU 24213) (16,26). That is not to say that seizure protection and behavioural excitation necessarily go hand in hand, as illustrated by the varying anticonvulsant profiles Loscher and Czuczwar (24) have obtained with PHNO and lisuride in different rodent models. Similarly, the complete lack of effect of SC RU 24213 on the development of pilocarpine-induced seizures, which we noted in the present study (Table 1), contrasts sharply with the head-down sniffing, hunched posture and forward locomotion elicited by this compound at the higher dose levels (1.5–4.5 mg/kg SC), which are indicative of central D-2 stimulation. Even when injected directly into the striatum, RU 24213 reduced only the severity and not the incidence of the convulsions (Fig. 1).

These results with RU 24213 are particularly illuminating, as RU 24213 was originally reported to be one of the most potent of a series of N-phenylethylamine derivatives (28), and has since been shown to perform only marginally less well than LY 171555 and apomorphine in biochemical (14), behavioural (34–36) and electrophysiological (43) tests of D-2 function. RU 24213's patent inefficacy in the pilocarpine model of epilepsy, in doses clearly adequate to activate D-2 receptors in the brain, is perhaps mute testimony to the existence of functionally separate central D-2 receptors: one mediating the anticonvulsant and another the behavioural response to D-2 agonists. Future experimentation will address this issue, but in the meantime we would point out that a functional dichotomy of this sort already exists within the D-1 receptor group. D-1 receptors in the nigra appear only capable of facilitating seizure activity (3, 4, 15), whereas those in the forebrain can additionally mediate changes in the animal's normal pattern of motor behaviour (9, 15, 29, 33).

In conclusion, the present study completes the topographic picture of dopamine's involvement in D-1- and D-2-dependent modulation of seizure activity within the framework of the nigrostriatal dopamine system. It is envisaged that the release of endogenous dopamine from axon terminals attenuates the propagation of limbic motor seizures by engaging appropriate D-2 receptors in the striatum, while dendritically released dopamine has the opposite effect and potentiates seizure spread, via D-1 receptors in the nigra.

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