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Blockade of Photically Induced Epilepsy by 'Dopamine Agonist' Ergot Alkaloids

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Abstract. The effect of the intravenous administration of ergot alkaloids on epileptic responses to intermittent photic stimulation (IPS) has been studied in adolescent baboons, *Papio papio*, from Senegal. Ergocornine, 1–2 mg/kg, produced marked autonomic and behavioural effects, slowed the EEG, and abolished myoclonic responses to IPS for 30–90 min. Ergometrine, 1 mg/kg, activated the EEG and blocked the induction of myoclonic responses for 1–3 h. Bromocriptine, 0.5–4 mg/kg, did not consistently prevent myoclonic responses to IPS. After pretreatment with a subconvulsant dose of allylglycine (180–200 mg/kg), lysergic acid diethylamide, 0.1 mg/kg, retained the capacity to block myoclonic responses to IPS, and ergocornine 1 mg/kg reduced such responses. The convulsant effect of allylglycine was enhanced, however, so that prolonged seizure sequences began 19–96 min after ergocornine administration. The protective action of ergot alkaloids against epileptic responses induced by sensory stimulation is interpreted in terms of effects at several sites, including dopaminergic and serotoninergic synapses.

Key words: Ergot alkaloids – Reflex epilepsy – Photosensitive baboons – Dopamine – Allylglycine – Ergocornine

Various ergot derivatives have been shown to block photically induced epileptic responses in the Senegalese baboon, *Papio papio* (Walter et al., 1971; Meldrum and Naquet, 1971; Vuillon-Cacciuttolo and Balzano, 1972). This effect appears at least partially attributable to diminution of synaptic transmission in the lateral geniculate body by a serotoninlike action of the compounds (Aghajanian et al., 1972; Curtis and Davis, 1962). Thus, after lysergic acid diethylamide (LSD), the reduction in amplitude of the earliest wave of the visual evoked response in the lateral geniculate body or occipital cortex correlates well with the reduction in photosensitivity (Vuillon-Cacciuttolo et al., 1973). In addition to the evidence for serotonin agonist and antagonist actions of ergot alkaloids in the CNS, it has recently been demonstrated that some ergot derivatives interact with cerebral dopamine (DA) receptors. Thus several ergot alkaloids stimulate dopamine-sensitive adenylate cyclase (von Hungen et al., 1974; da Prada et al., 1975) and modify motor activity in intact or brain-lesioned rats in ways indicative of dopaminergic activation (see Discussion).

We previously reported that the dopamine agonist apomorphine reduces photically induced epilepsy in *Papio papio* (Meldrum et al., 1975a) and that ergot alkaloids which cause contralateral turning in mice with unilateral lesions of the nigrostriatal pathway reduce the severity of audiogenic seizures in an inbred strain of mice (Anlezark et al., 1976). We now report the effects of ergocornine, bromocriptine, and ergometrine on behaviour, EEG, and photically induced epilepsy in the baboon.

The syndrome of photically induced epilepsy can be enhanced by subconvulsant doses of allylglycine (Meldrum et al., 1975b), a compound that leads to inhibition of cerebral glutamic acid decarboxylase activity (Horton and Meldrum, 1973). Most clinically useful anticonvulsant drugs are effective in this test system (Meldrum et al., 1975b), but apomorphine not only loses its anticonvulsant properties, but also tends to augment the epileptogenic effects of allylglycine (Meldrum et al., 1975a). We therefore compared the actions of LSD and ergocornine in baboons pretreated with subconvulsant doses of allylglycine to explore the possibility that this test system differentiates anticonvulsant effects primarily dependent on serotoninergic mechanisms from those dependent on dopaminergic actions.

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MATERIALS AND METHODS

Thirteen adolescent baboons, *Papio papio*, from the Casamance region of Senegal, were used in 35 experiments. The animals were seated in primate restraining chairs, and the EEG was recorded on a Galileo SLE 18 channel EEG machine via 15 chronically implanted epidural electrodes (Meldrum et al., 1975a). Stroboscopic stimulation at 20–35 flashes/s was provided by a Dawe Strobotorch held 20 cm from the animals' eyes. Standardised tests lasting 5 min were conducted before and 10–30 min after drug or vehicle administration, and then at hourly intervals for up to 6 h. In eight experiments a subconvulsant dose of allylglycine, 180–200 mg/kg, was given 200 min before administration of LSD or ergocornine. Myoclonic responses were graded as follows: 0 = no response, 1 = eyelid myoclonus, 2 = myoclonus of facial and neck muscles, 3 = myoclonus of all four limbs, 4 = myoclonus continuing beyond the end of photic stimulation, S = tonic-clonic seizure. At least 1 week intervened between drug tests in any one animal.

Drugs. The following drugs were used: 2-bromo-α-ergocryptine methanesulphonate(bromocriptine), ergocornine hydrogenmaleinate, D-lysergic acid diethylamide tartrate (LSD) (Sandoz), ergonovine maleate (ergometrine), and D,L-2-amino-4-pentenoic acid (allylglycine) (Sigma).

Ergocornine and bromocriptine were dissolved, with an equal weight of tartaric acid, in a few drops of 70% ethanol and made up to volume with warm saline. Ergometrine, LSD, and allylglycine were dissolved in saline.

Drugs (or vehicle) were injected i.v.

RESULTS

Autonomic and Behavioural Effects. Ergocornine, ergometrine, and bromocriptine induced pupil dilatation within 1–10 min of administration. Within 1 min of ergocornine, 1–2 mg/kg (or 10 min ergocornine 0.5 mg/kg), ptosis, with the eyes rolled up, and some chewing and licking were observed. Ergocornine also induced, after 5–10 min, profuse salivation, loss of muscle tone, and absence of visual following. After 2 h, alert behaviour with spontaneous limb movements returned.

Ergometrine, 0.4 and 1 mg/kg, induced licking and chewing 1–2 min after administration. Aggressive and agitated behaviour with irregular cries subsequently occurred and were accompanied by piloerection. This condition lasted for up to 1 h and was severe after 1 mg/kg.

The main behavioural effect seen after bromocriptine (0.5–4 mg/kg) was yawning, lip-smacking, and opening of the mouth. Aggressive responses became difficult to elicit. Animals were very restless 3 h after administration of 2 or 4 mg/kg.

EEG Changes. Ergocornine, 0.5–2.0 mg/kg, induced high-voltage slow activities within a few seconds of i.v. administration. Enhancement of slower background rhythms was still evident 2–3 h later. EEG spikes and waves were absent during photic stimulation 30 min after ergocornine, 1–2 mg/kg. Paroxysmal EEG responses during photic stimulation 3.5 h after drug administration were similar to predrug responses.

After ergometrine, 0.4–1.0 mg/kg, an increase in the proportion of irregular fast activity on the EEG was associated with a reduction in the incidence of spontaneous spikes and waves, lasting 2–3 h. EEG paroxysmal responses to photic stimulation were absent 1.5 h after ergometrine, 1 mg/kg.

Slowing of the EEG background rhythms was seen within 10 min of the administration of bromocriptine, 1–4 mg/kg. Subsequently, the incidence of spontaneous spikes and waves was reduced. The enhanced slow activity continued for 2–3 h after bromocriptine, 4 mg/kg. A reduction in the incidence of photically induced spikes and waves was most marked after 1.5–2.5 h.

Photically Induced Myoclonus. The effects of ergocornine, ergometrine, and bromocriptine (or saline) on photically induced myoclonic responses are shown in Table 1.

The loss of responsiveness to photic stimulation after ergocornine was clearly dose-dependent. A slight transient reduction in myoclonic responses was seen 30 min after ergocornine 0.5 mg/kg, whereas none of the animals treated with 1 mg/kg showed myoclonic responses at this interval after drug administration. A more prolonged effect was seen after 2 mg/kg.

Ergometrine also reduced myoclonic responses to photic stimulation in a dose-dependent way. All three doses (0.15, 0.4, and 1 mg/kg) were administered to the most photosensitive animal (SB 49) who consistently showed a sustained epileptic response (4 or 5) in control tests. No definite drug-induced reduction in photosensitivity was seen in this animal after 0.15 mg/kg. (The decrease after 150–180 min is probably a result of the tonic-clonic seizure at 90 min, which is often followed by a refractory state in which the animal is less responsive.) A slight, transient diminution in myoclonic responses was seen 30 min after 0.4 mg/kg, whereas after 1 mg/kg the responses were absent at 90 min and considerably reduced for up to 150 min. In baboon PD 8, myoclonic responses were reduced or, at times, absent after all the doses. (In this animal responsiveness did not return to control after the two higher doses.)

Reductions in myoclonic responses observed after bromocriptine, 0.5, 1, 2, and 4 mg/kg, were not uniformly related to the dose. In the most photosensitive animal, SB 49 (given 1 and 2 mg/kg), only a slight transient reduction in myoclonic responses occurred (the reduction after 1 mg/kg is possibly related to the tonic-clonic seizure at 30 min). Both animals given 4 mg/kg showed reductions in responsiveness (compared to control tests and saline experiments).

Table 1
Effect of ergot alkaloids on myoclonic responses to photic stimulation in *Papio papio*

Drug	Baboon	Control	Response to photic stimulation after injection (min)					
			30	90	150	210	270	330
Saline	SB49	4	4	4	4	4	4	4
	SB54	3	3	3	3	3	3	3
	SB71	2	2, 3	1	0, 1	0, 1	0	0
	SB75	2, 3	1	2	0	2	0	0
	PD8	3	3	3	3	2, 3	3	1
	PD13	1	0	0, 1	0, 1	0	0, 1	
Ergocornine								
0.5	PD13	3	2, 3	3	3	3	3	
0.5	SB71	3	1	3	3	3	2, 3	2
1.0	PD8	4	0	0	3	3	3	3
1.0	SB49	4	0	3	3, 4	4	3, 4	S
1.0	SB75	3, 4	0	2, 3	3	3	3	3
2.0	PD13	3	0	0	1, 2	3	3	3
2.0	SB54	3, 4	0	0, 1	0, 1	1, 2	1	
Bromocriptine								
0.5	PB8	4	3	1, 2	3	2, 3	3	3
0.5	PD13	1	1	0, 1	0	0, 1	1	1
1.0	SB54	4	1	1	1	1	1	1
1.0	SB49	4	S	3	3	4	4	4
1.0	PD13	1, 2	1, 2	1	0, 1	1	1	1
2.0	SB75	3	1, 2	1	0, 1	0, 1	1	0
2.0	PD8	4	1	1	0, 1	0, 1	0	0, 1
2.0	PD13	3	1	2	3	3	3	3
2.0	SB49	4	4	4	3	4	4	4
4.0	PD8	4	2, 3	1	1	1	1	
4.0	SB75	3	1	0, 1	0	0	0, 1	0
Ergometrine								
0.15	PD8	3	1	2	2	2	2	2, 3
0.15	SB49	4	4	S	3	1, 2	3	1
0.4	SB49	4	3	4	4	4	4	4
0.4	PD8	1, 2	0	0	0, 1	0, 1	1	1
1.0	SB49	4	0, 1	0	0, 1	3	4	4
1.0	PD8	3	0	0	0	0	0	0

Tests with a stroboscope were performed before and after the i.v. injection of saline, ergocornine (0.5–2.0 mg/kg), bromocriptine (0.5–4.0 mg/kg), or ergometrine (0.15–1.0 mg/kg). Responses were graded as described in the text (where two grades of response are shown, the more severe response was seen only once or very transiently)

No return to control responsiveness was seen, suggesting a prolonged duration of drug action.

Allylglycine Pretreatment (Table 2). Both an anticonvulsant and a proconvulsant effect were seen when LSD or ergocornine were given 200 min after pretreatment with a subconvulsant dose of allylglycine. Photically induced myoclonic responses were abolished 10 min after LSD, 0.1 mg/kg, and were reduced 30 min after ergocornine, 0.5–1.0 mg/kg. [Responses 210–230 min after allylglycine, 180–200 mg/kg, are equal to, or more commonly greater than, those induced by photic stimulation 160 min after allylglycine (Meldrum et al., 1975b).]

The combination of allylglycine and ergocornine resulted, however, in an enhancement of the effects of both drugs. The immediate autonomic, behavioural, and EEG effects of ergocornine were more severe; ergocornine 1.0 mg/kg, after allylglycine produced changes as great, or greater, than those seen after ergocornine, 2.0 mg/kg given alone. The tendency for allylglycine to induce seizures (without a specific sensory trigger) was enhanced and modified after ergocornine. Two animals manifested generalised seizures, with initial eyelid myoclonus, tonic spasm, rhythmic myoclonus of the limbs, and postictal depression (starting 96 and 19 min after ergocornine). In each case this was followed by a closely spaced sequence of similar seizures, without full recovery between seizures. In baboon SB 75 EEG seizure activity was continuous for 20 min. (In both animals the sequence was therapeutically terminated after 6 seizures by the injection of diazepam 2 mg.)

DISCUSSION

In this animal model, ergocornine and ergometrine are approximately equipotent against photically induced myoclonus. Their potency is similar to that of

Table 2. Effect on photically induced myoclonic responses of (A) LSD, 0.05–0.1 mg/kg, or (B) ergocornine, 0.5–1.0 mg/kg, given i.v. 200 min after injection of D,L-allylglycine, 180–200 mg/kg

A. LSD

Baboon	Control response	Response after allylglycine			LSD dose (mg/kg)	+ 210 min	+ 270 min
		+ 30 min	+ 100 min	+ 160 min			
SB 79	0, 1	1, 2	3	4	0.05	1, 2	4 (ss + 100)
SB 80	2	0	4	4	0.07	S (ss + 15)	4
SB 78	0, 1	0, 1	2	3, 4	0.1	0	S
SB 77	4	3	3	4	0.1	0	3

B. Ergocornine

Baboon	Control response	+ 40 min	+ 100 min	+ 160 min	Ergocornine (mg/kg)	+ 230 min	+ 290 min	+ 350 min
SB 81	0	0	0, 1	3	0.5	2, 3	S	4
SB 76	2	1, 2	4	4	0.7	3	S	(ss + 96 + 101 + 106 + 108)
SB 75	1, 2	2	2, 3	3	1.0	(ss + 19, + 27, + 39–59, + 65, + 73, + 76)		
SB 73	1, 2	0, 1	3	3	1.0	2	3	3

Testing performed and responses graded (0–4, or S) as described in the text. Spontaneous seizures indicated by ss + time in min after administration of LSD or ergocornine

methylergometrine (Vuillon-Cacciuttolo and Balzano, 1972) and is at least four times as great as that of bromocriptine. In this respect photic epilepsy in the baboon differs from the other animal model of reflex epilepsy – audiogenic seizures in mice – in which ergocornine is 5 times as potent as bromocriptine and 5–10 times as potent as ergometrine (Anlezark et al., 1976). The sensitivity to LSD also differs markedly for the two syndromes of reflex epilepsy, LSD blocks myoclonic responses in baboons at 0.05–0.1 mg/kg (Walter et al., 1971), but blockade of audiogenic seizures in mice requires 10 mg/kg (Anlezark et al., 1976).

Ergot alkaloids have been shown to act as agonists at central DA receptors in several behavioural test systems. In rodents with unilateral lesions in the nigrostriatal dopaminergic pathway, turning away from the lesioned side is observed following ergocornine (Corrodi et al., 1973; Anlezark et al., 1976; Pieri et al., 1975), ergometrine (Pieri et al., 1975; Woodruff et al., 1974; Anlezark et al., 1976), and bromocriptine (Corrodi et al., 1973; Anlezark et al., 1976; Pieri et al., 1975). Such behaviour is blocked by neuroleptic administration, but not (in the case of ergocornine and ergometrine) by inhibition of catecholamine synthesis, suggesting an agonist action of these drugs at postsynaptic DA receptors. Stereotyped behaviour in rats and increased locomotor activity in mice, which both result from dopaminergic stimulation, are induced by ergocornine (Johnson et al., 1973), ergometrine (Pijnenburg et al., 1973), and bromocriptine (Johnson et al., 1976; Snider et al., 1975).

In biochemical experiments these ergot alkaloids bind to DA receptors in striatal membranes with similar potency ratios to those seen in behavioural tests (Burt et al., 1976) and stimulate production of cyclic AMP in striatal homogenates in vitro or in vivo (Elkhawad et al., 1975; von Hungen et al., 1974; Trabucchi et al., 1976).

Ergocornine and bromocriptine reduce DA turnover as measured by the decelerated disappearance of DA from the brain after catecholamine synthesis inhibition (Fuxe et al., 1974).

In other experiments we have shown that ergocornine and bromocriptine reduce DA turnover in mouse brain while protecting mice against audiogenic seizures (Anlezark et al., unpublished), but ergometrine, like LSD, has a weak effect on both seizure response and DA metabolism. The protective action of ergocornine against audiogenic seizures can be blocked by the DA antagonist haloperidol. This evidence strongly suggests that ergot alkaloids can protect against audiogenic seizures in mice by an agonist action on postsynaptic DA receptors. That stimulation of cerebral DA receptors can reduce photically induced myoclonus in baboons is indicated by the finding that apomorphine or n-propylnorapomorphine abolish responses to IPS 15 min after their administration (Meldrum et al., 1975; Ashton et al., 1976). Ergotalkaloids, however, also have marked effects on central 5-HT neurons. Thus the alteration in afferent visual transmission produced by LSD is apparently the result of altered activity in a serotonin-

ergic system acting on neurons in the lateral geniculate body (Walter et al., 1971; Aghajanian, 1972; Vuillon-Cacciuttolo et al., 1973). The greater potency of LSD against photically induced epilepsy relative to ergocornine and ergometrine in baboons, and their very different relative potency against audiogenic seizures in mice, is probably due in part to this effect on the visual afferent system.

The inhibition of photically induced myoclonus seen in baboons after administration of ergot alkaloids is the result of various pharmacological actions at numerous sites in the brain. Among these pharmacological actions is activation of dopamine receptors, although we do not know which anatomical system is most significantly involved in the antiepileptic effect. There is also the complicating possibility of two DA receptors, suggested by the fact that some dopamine-mediated effects can be blocked by ergot alkaloids (Cools et al., 1976). Actions on serotoninergic systems are also important; actions at the level of the lateral geniculate, or perikaryal receptors of neurons in the nuclei of the dorsal raphe, and on receptors on cortical neurons may all be involved. Evidently the ratio of their activities (and other potentially relevant actions) varies between the different ergot derivatives.

Interaction Between Allylglycine and Ergot Alkaloids. The proconvulsant action of allylglycine is related to inhibition of cerebral glutamic acid decarboxylase by 2-keto-4-pentenoic acid (Horton and Meldrum, 1973; Orlowski et al., 1977; Horton et al., unpublished) a metabolite arising through the action of transaminases or oxidases on allylglycine. The preservation of the protective action of LSD (and to a lesser extent, of ergocornine) against photically induced epilepsy can be explained in terms of action at a serotoninergic synapse in the lateral geniculate. (Impairment of afferent transmission by LSD presumably does not depend on normal functioning of GABA-mediated postsynaptic inhibition.) LSD and ergocornine might also be acting on a retinal dopaminergic system (Da Prada et al., 1975), but electrophysiological data (Vuillon-Cacciutolo et al., 1973) indicates that, at least for LSD, the more significant impairment of afferent transmission occurs at the level of the lateral geniculate body.

Within the basal ganglia, an interaction between GABA-mediated inhibition and dopaminergic systems has been demonstrated by electrophysiological, biochemical, and behavioural means. In general, blockade of GABA inhibition enhances dopaminergic effects, e.g., injection of picrotoxin, a GABA receptor blocker, unilaterally into the substantia nigra induces turning in the rat (Tarsy et al., 1975), and enhancement of GABAergic effects diminishes them, e.g., muscimol, a GABA agonist, prevents the enhanced motility induced by the injection of ergometrine into the nucleus accumbens in the rat (Scheel-Krüger et al., 1977) or injection of ethanolamine-0-sulphate, which increases GABA content by inhibiting GABA transaminase activity, provokes turning in rats or mice when injected into the striatum or substantia nigra (Horton and Pycock, 1977). The enhancement of the behavioural and autonomic effects of ergocornine after allylglycine pretreatment is thus probably due to impairment of a GABA-mediated negative feedback that is normally activated following dopamine agonist activity.

We earlier reported the occurrence of seizures without sensory provocation in baboons 2–3 min after apomorphine, 1 mg/kg, when given 2.75 h after allylglycine, 180–200 mg/kg. This phenomenon and the rapid repetition of seizures once initiated following 'subconvulsant' doses of allylglycine and ergocornine, 0.7–1.0 mg/kg, are not readily explicable in terms of identified GABA-dopamine interactions. It appears, however, that excessive activation of some dopamine receptors impairs a mechanism that normally allows partial compensation for a diminished rate of GABA synthesis.

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