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DOPAMINE AGONISTS AND AUDIOGENIC SEIZURES: THE RELATIONSHIP BETWEEN PROTECTION AGAINST SEIZURES AND CHANGES IN MONOAMINE METABOLISM

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Abstract—Apomorphine (1 and 10 mg/kg), (−) *N*-*n*-propylnorapomorphine, (NPA, 0.1 mg/kg) ergot alkaloids (ergocornine, 2 mg/kg; bromocryptine, 10 mg/kg; *d*-lysergic acid diethylamide, LSD, 9 mg/kg; ergometrine, 4 and 10 mg/kg), and quipazine (50 mg/kg) protect DBA/2 mice against sound-induced seizures, although LSD, ergometrine, and quipazine do not prevent the initial wild running seizure response. The order of potency for prevention of the clonic phase of the seizure response is NPA > ergocornine ⩾ apomorphine > bromocryptine > LSD ⩾ ergometrine > quipazine. Apomorphine (10 mg/kg) increases dopamine (+72%) and noradrenaline (+91%) content after 15 min. Apomorphine, NPA and the ergot alkaloids reduce cerebral concentration of homovanillic acid (HVA) (by 31–73 per cent), but with a longer time course than the seizure protection (maximal reduction after 1–3 hr). After LSD, ergometrine and quipazine a fall in 5-hydroxyindoleacetic acid content (by 35–48 per cent) occurs before the fall in HVA content. All the drugs except quipazine lower body temperature (maximum decrease 6.9° after apomorphine 10 mg/kg). The greatest decrease in temperature occurs at the time of maximal protection against seizures. A protective effect of the ergot alkaloids (LSD and ergocornine) was still apparent when the fall in temperature was prevented by external heating. The anti-epileptic action of ergocornine, bromocryptine and the apomorphine derivatives is associated with stimulation of receptors pharmacologically equivalent to the DAe receptors of Cools *et al.*, 1976 (i.e. activated by dopamine and apomorphine, blocked by haloperidol).

We have previously shown that drugs believed to act as agonists at central dopamine (DA) receptors reduce seizures induced by photic stimulation in the baboon, *Papio papio*, [1] and audiogenic seizures in genetically susceptible mice [2]. In mice, with unilateral lesions of the nigro-striatal pathway, the potency of such drugs to induce contralateral rotation is similar to their ability to reduce audiogenic seizure susceptibility [3]. This indication of an effect of dopaminergic activity on reflex epilepsy is supported by the findings that *L*-DOPA blocks reserpine-induced enhancement of audiogenic seizures [4] and that haloperidol, a DA receptor antagonist [5], blocks the protective effect of apomorphine and ergocornine against audiogenic seizures [3].

Although ergot alkaloids have been shown to possess DA agonist properties in behavioural [3, 6–8] and biochemical [6, 9] experiments, they are also thought to interact with other central monoamines, particularly 5-hydroxytryptamine (5 HT) [10, 11].

In the present study we have compared the anti-epileptic actions of dopamine agonists (apomorphine and *n*-propylnorapomorphine, NPA), ergot alkaloids and a serotoninergic agonist (quipazine) in DBA/2 mice. The time course of this action has been correlated with the time course of changes in cerebral monoamine metabolism, as indicated by the cerebral concentrations of 5HT, DA, Noradrenaline (NA) and the metabolites 5-hydroxyindole acetic acid (5-HIAA) and homovanillic acid (HVA).

MATERIALS AND METHODS

DBA/2 mice, of either sex, weight 7–13 g, 23–27 days old, were used in all experiments. Groups of at least 10 mice were injected i.p. (0.1 ml) with drug or vehicle and the response to auditory stimulation was evaluated at the following times: apomorphine (1 and 10 mg/kg, diluted with saline) at 15 min, 30 min, 1 hr, and 2 hr; ergocornine (2 mg/kg, dissolved with an equal weight of tartaric acid in a few drops of 70% ethanol, and diluted with saline), ergometrine (4 and 10 mg/kg, dissolved in saline), bromocryptine (10 mg/kg, dissolved as for ergocornine), lysergic acid diethylamide (LSD, 9 mg/kg, dissolved in saline) (−)*N*-*n*-propylnorapomorphine (NPA, 0.1 mg/kg, dissolved in saline containing 0.1% sodium metabisulphite bubbled with nitrogen and diluted with saline) at 30 min, 1, 2 and 3 hr; and quipazine (50 mg/kg, dissolved in saline) at 1, 2 and 4 hr. The doses were chosen in relation to the ability of the drugs to block the clonic phase of the seizure in 50 per cent of animals [3]. Individual animals were placed under a Perspex dome (diameter 58 cm) and 30 sec allowed for habituation. Auditory stimulation (109 dB) was applied for 60 sec or until tonic extension occurred. The seizure response (S.R.) to auditory stimulation

was scored as previously described (1 = running, 2 = clonic phase, 3 = tonic phase, [3]). Auditory stimulation was carried out at the same time of day (10.00–13.00 hr) in all experiments. Rectal temperatures were measured before drug administration and again immediately before auditory stimulation. In some experiments the mouse cage was kept in a thermostatically-controlled chamber between injection and testing.

Directly after testing, the mice were killed by decapitation and the whole brains were rapidly removed and frozen in liquid nitrogen. Estimations of DA, HVA, 5HT, 5-HIAA, and NA were carried out as previously described [12]. Estimations of biochemical changes in the brains of drug-treated mice are expressed as a per cent of the values from control mice assayed concurrently. Statistical comparisons were made using Student's *t*-test (biochemical changes) or Fisher's exact probability test (seizure response).

The drugs used were: apomorphine hydrochloride B.P. (Evans Medical), (−)*N*-*n*-propylnorapomorphine hydrochloride (a gift from Professor J. L. Neumeyer), lysergic acid diethylamide tartrate (LSD, 25 Delysid, Sandoz), Ergometrine maleate (Sigma Chemical Co), Ergocornine hydrogenmaleinate and

Table 1. Effect of drugs on the incidence of seizure phases

Drug and dose	Time	Running	Per cent response clonic	Tonic	Mean S.R. ±S.E.M.
Apomorphine	0	100	100	100	3
1 mg/kg	15 min	80	40*	30†	1.5 ± 0.4
	30 min	90	70	70	2.3 ± 0.4
	1 hr	100	100	80	2.8 ± 0.1
	2 hr	90	90	80	2.6 ± 0.3
Apomorphine	0	100	100	87	2.9 ± 0.1
10 mg/kg	15 min	7†	7†	7†	0.2 ± 0.2
	30 min	27†	13†	0†	0.4 ± 0.2
	1 hr	80	67*	60	2.1 ± 0.3
	2 hr	87	87	80	2.5 ± 0.3
NPA	0	100	100	100	3
0.1 mg/kg	30 min	40*	20†	0†	0.6 ± 0.3
	1 hr	80	70	60	2.1 ± 0.4
	2 hr	100	100	100	3
	3 hr	100	60	60	2.2 ± 0.3
Ergocornine	0	100	100	100	3
2 mg/kg	30 min	20†	10†	0†	0.3 ± 0.2
	1 hr	70	30†	0†	1.0 ± 0.3
	2 hr	80	40*	0†	1.2 ± 0.2
	3 hr	100	100	0†	2
Bromocryptine	0	100	100	90	2.9 ± 0.1
10 mg/kg	30 min	50*	0†	0†	0.5 ± 0.1
	1 hr	30*	0†	0*	0.3 ± 0.2
	2 hr	90	50*	50	1.9 ± 0.4
	3 hr	90	80	80	2.5 ± 0.3
LSD	0	100	93	73	2.7 ± 0.2
9 mg/kg	30 min	80	27†	7†	1.3 ± 0.2
	1 hr	100	87	27†	2.1 ± 0.1
	2 hr	93	53	20†	1.7 ± 0.2
	3 hr	87	47*	7†	1.4 ± 0.2
Ergometrine	0	100	100	93	2.9 ± 0.1
4 mg/kg	30 min	100	93	53*	2.5 ± 0.2
	1 hr	100	87	60	2.5 ± 0.2
	2 hr	100	93	80	2.7 ± 0.1
	3 hr	100	100	100	3
Ergometrine	0	94	89	83	2.7 ± 0.2
10 mg/kg	30 min	93	73	47	2.1 ± 0.2
	1 hr	100	86	64	2.5 ± 0.2
	2 hr	93	73	73	2.4 ± 0.3
	3 hr	100	87	80	2.7 ± 0.2
Quipazine	0	90	90	80	2.6 ± 0.3
50 mg/kg	1 hr	100	100	60	2.6 ± 0.2
	2 hr	90	60	20*	1.7 ± 0.3
	4 hr	80	70	0†	1.5 ± 0.3

Groups of mice were injected i.p. with drugs and exposed to auditory stimulation after the times shown. The incidence of each seizure phase is expressed as the percent of mice in each group (n = 10–15). Significant differences in the incidences of the seizure stages between control and drug-treated animals (Fisher's exact probability test) are denoted by: * $P < 0.05$, † $P < 0.01$. Mean S.R. is the arithmetic mean of maximal individual responses scored as described in methods.

2-bromo-ergocryptine methanesulphonate (CB 154, bromocryptine) Sandoz) and Quipazine (2-(-piperazinyl) quinoline maleate, Miles Laboratories). All doses are expressed as weight of salt.

RESULTS

Apomorphine. After apomorphine (1 mg/kg) mice were significantly protected only against the clonic ($P < 0.05$) and tonic ($P < 0.01$) phases of the seizure at 15 min (Table 1), whereas significant protection against all phases was seen 15 min and 30 min following 10 mg/kg. The incidence of clonic phase remained significantly reduced 1 hr after apomorphine 10 mg/kg.

A fall in rectal temperature was seen after both doses of apomorphine (maximal: 4.1°, 15 min after 1 mg/kg and 6.9°, 30 min after 10 mg/kg; Table 2). After 10 mg/kg, rectal temperature remained significantly reduced compared to controls for at least 2 hr. Mice kept at 35° after apomorphine 10 mg/kg showed an elevated rectal temperature (+1.1°) and no protection against seizures (Table 3).

Apomorphine induced changes in DA and HVA content which were dependent on dose (Table 4). DA was elevated 30 min after 1 mg/kg (47 per cent) and 15 min after 10 mg/kg (72 per cent) and was unchanged at other times, except for a decrease (33 per cent) 2 hr after 1 mg/kg. HVA was decreased 1 hr after 1 mg/kg (31 per cent) and at all times following 10 mg/kg (maximally 72 per cent at 2 hr). Apomorphine 1 mg/kg elevated 5HT (maximum 26 per cent at 1 hr) but no change was seen after 10 mg/kg. A fall in 5-HIAA occurred after 1 mg/kg (maximum 39 per cent after 2 hr), while an increase (27 per cent) was seen 30 min after 10 mg/kg. NA was unchanged after 1 mg/kg, but was elevated (90 per cent) 15 min after 10 mg/kg.

NPA. NPA (0.1 mg/kg) significantly decreased the incidence of all phases of the seizure response at 30 min (Table 1). Rectal temperatures were reduced at 30 min, 1 hr and 3 hr, with the maximum decrease at 30 min (4.8°, Table 2).

HVA was reduced after NPA at all times tested (maximum decrease 47 per cent) at 30 min and 2 hr, Table 4). Similarly, DA was significantly decreased in the first hour and at 3 hr (maximally 38 per cent at 3 hr). No effect was seen on whole brain concentrations of 5HT or NA, but 5-HIAA was reduced after 30 min (17 per cent) and increased after 3 hr (11 per cent).

Ergocornine. Ergocornine (2 mg/kg) reduced the incidences of tonic phase for 3 hr, clonic phase for 2 hr and wild running for 30 min (Table 1). The maximum decrease in S.R. occurred at 30 min.

Rectal temperatures were significantly reduced compared to controls for 1 hr (Table 2). Mice kept at an environmental temperature of 35° showed marked protection against audiogenic seizures 30 min after ergocornine 2 mg/kg (Table 3).

Ergocornine had no significant effect on brain DA concentrations (Table 4) whereas its metabolite, HVA, was significantly decreased (55–63 per cent) at all times after drug administration. Brain 5HT concentrations remained at control levels for 2 hr, but fell to 89 per cent of the control at 3 hr. A decrease in 5-HIAA (maximally 54 per cent at 2 hr) was seen at all times. NA was reduced significantly after 1 hr.

Table 2. Effect of drugs on mean rectal temperature

Drug and dose	Time	Change in temp (°)	Drug and dose	Time	Change in temp (°)
Apomorphine	15 min	−4.1 ± 0.7†	LSD	30 min	−1.1 ± 0.5†
1 mg/kg	30 min	−3.1 ± 0.6†	9 mg/kg	1 hr	−1.3 ± 0.6†
	1 hr	−1.0 ± 0.2†		2 hr	−1.5 ± 0.7*
	2 hr	−0.9 ± 0.2		3 hr	−1.2 ± 1.0
Apomorphine	15 min	−6.5 ± 0.1†	Ergometrine	30 min	−3.1 ± 0.5†
10 mg/kg	30 min	−6.9 ± 0.4†	4 mg/kg	1 hr	−2.5 ± 0.9†
	1 hr	−3.9 ± 0.4†		2 hr	−2.2 ± 0.7†
	2 hr	−2.0 ± 0.3†		3 hr	−2.6 ± 0.8*
NPA	30 min	−4.8 ± 0.1†	Ergometrine	30 min	−1.6 ± 0.3†
0.1 mg/kg	1 hr	−1.4 ± 0.2†	10 mg/kg	1 hr	−3.1 ± 0.2†
	2 hr	0 ± 0.1		2 hr	+0.4 ± 0.5
	3 hr	−0.6 ± 0.1†		3 hr	+0.4 ± 0.5
Ergocornine	30 min	−4.4 ± 0.3†	Quipazine	1 hr	−0.5 ± 0.1
2 mg/kg	1 hr	−3.6 ± 0.5†	50 mg/kg	2 hr	−0.1 ± 0.2
	2 hr	−1.3 ± 0.5		4 hr	+0.2 ± 0.2
	3 hr	−1.0 ± 0.3			
Bromocryptine	30 min	−5.5 ± 0.6†			
10 mg/kg	1 hr	−5.8 ± 0.6†			
	2 hr	−5.0 ± 0.8†			
	3 hr	−3.8 ± 0.6†			

Rectal temperatures of groups of mice (n = 5–10 for each group) were measured and the mice injected with drug or saline. Rectal temperatures were measured again at the stated times. Animals were maintained in an ambient temperature of 22–28°. The results are expressed as mean change (±SEM) in rectal temperature (°). The statistical significance of the change was evaluated by comparison with the mean change in the concurrent (saline) control group (which in no case exceeded 1°). * $P < 0.5$; † $P < 0.01$.

Table 3. Rectal temperature and drug-induced change in seizure response

Drug and dose		Rectal temperature	Running	Per cent response clonic	Tonic	Mean SR
Saline	Room temperature	37.1 ± 0.1	100	100	100	3
LSD 9 mg/kg	Room temperature	35.3 ± 0.2†	100	10†	0†	1.1 ± 0.1
	Chamber (30°)	37.0 ± 0.1	100	60	50*	2.1 ± 0.3
Saline	Room temperature	36.0 ± 0.3	100	100	100	3
Ergocornine 2 mg/kg	Room temperature	32.0 ± 0.2†	59†	6†	0†	0.6 ± 0.1
	Chamber (35°)	36.9 ± 0.1†	88	25†	25†	1.4 ± 0.3
Saline	Room temperature	36.8 ± 0.1	100	100	100	3
Apomorphine 10 mg/kg	Room temperature	31.8 ± 0.3†	38†	13†	0†	0.5 ± 0.3
	Chamber (35°)	37.9 ± 0.2†	100	100	100	3

Matched groups of mice (n = 8–18) were injected with saline or drug and kept either at room temperature (22–25°) or in a thermostatically controlled chamber (either 30 or 35°). Rectal temperatures (mean ± S.E.M.) and seizure response were determined 30 min after injection. Significant differences between seizure responses in saline and drug-treated animals (Fisher's exact probability test) are denoted by * $P < 0.05$, † $P < 0.01$. Significant differences between mean rectal temperature in saline and drug treated animals (Student's t-test) are denoted by † $P < 0.01$. Mean S.R. is the arithmetic mean (±S.E.M.) of maximal individual responses scored as described in methods.

Bromocryptine. All the seizure stages were significantly reduced for 1 hr after bromocryptine 10 mg/kg (the clonic and tonic phases being absent) and the incidence of clonic phase was still reduced after 2 hr (Table 1). There was a sustained fall in rectal temperature following bromocryptine administration (Table 2).

Bromocryptine had no effect on brain concentrations of DA, 5HT or NA, except for a 10 per cent decrease in DA at 3 hr (Table 4). HVA was reduced at all times (maximally 54 per cent at 1 and 3 hr) whereas 5-HIAA was decreased for up to 1 hr (maximally 27 per cent at 30 min).

LSD. There was a significant decrease in the incidences of the clonic and tonic phases for 3 hr (except for the clonic phase at 1 hr) after LSD 9 mg/kg. No significant change in the incidence of wild running occurred at any time (Table 1). There was a slight, but significant fall in rectal temperature (maximum 1.5°) for up to 2 hr (Table 2). Mice kept at 30° showed no fall in rectal temperature; protection against the tonic phase of seizure response was present, but reduced in comparison to mice showing a small drop in rectal temperature (Table 3).

LSD had significant effects on all the biochemical parameters measured (Table 4). DA was reduced after 2 hr (26 per cent) and 5HT after 2 and 3 hr (23–24 per cent). NA concentration increased by a maximum 14 per cent after 2 hr. HVA concentration fell for 1–2 hr (maximum decrease 53 per cent at 1 hr). There was also a fall in 5-HIAA at all times, with a maximum decrease of 48 per cent at 30 min.

Ergometrine. Ergometrine only had a significant effect on S.R. at 30 min after 4 mg/kg (a decrease in the incidence of tonic phase). A similar decrease was seen after 10 mg/kg, but this was not significant (Table 1). After ergometrine 4 mg/kg, a moderate, but sustained, fall in rectal temperature was seen. However, following 10 mg/kg an initial fall in temperature (up to 1 hr) was followed by an increase at 3 hr (Table 2).

The most marked effect of ergometrine (4 and 10 mg/kg) was to reduce brain 5-HIAA concentrations at all times (maximum decrease: 35 per cent at 1 hr after 4 mg/kg and 43 per cent at 30 min after 10 mg/kg (Table 4). DA was reduced after 4 mg/kg (20 per cent) but not by 10 mg/kg; and 5HT was unchanged after 4 mg/kg, but was increased (18 per cent) 1 hr after 10 mg/kg. NA was unchanged at all times after either dose. HVA was reduced by both doses but only reached significance 2 and 3 hr after 4 mg/kg.

Quipazine. Quipazine (50 mg/kg) had no effect on the incidence of seizure stages in the first hour after administration. After 2 and 4 hr the incidence of tonic phase was significantly reduced, but changes in the other phases did not reach significance (Table 1). Quipazine had no significant effect on body temperature. There was a significant increase in 5HT concentration for 1–4 hr (maximally 38 per cent at 2 hr). At the same time 5-HIAA concentration fell with a maximum decrease at 4 hr (Table 4). No significant change in DA concentration was seen, whereas HVA was reduced after 4 hr by 23 per cent. NA was also reduced after quipazine (15 per cent at 4 hr).

DISCUSSION

Audiogenic seizures. Table 5 permits comparison of the present results with our previous data on blockade of audiogenic seizures by dopamine agonists. The drug doses and time intervals used here were selected in relation to the previous data, but with slight adjustments to facilitate comparisons of the neurochemical changes. The impairment of audiogenic seizure responses reported (Table 1) corresponds exactly with our previous results, both in terms of peak effect and ED_{50} for the abolition of clonic phase, with the single exception of ergometrine (after ergometrine, 10 mg/kg, 73 per cent of mice showed a clonic phase, whereas 50 per cent was predicted). The order of potency given in Table 5 is thus confirmed except for a suggested change in ergometrine, i.e. NPA > ergocornine ⩾ apomorphine > bromocryptine > LSD ⩾ ergometrine > quipazine. This differs from the order of potency for induction of

Table 4. Effect of drugs on monoamine metabolism

Drug and dose	Time	DA	HVA	5-HT	5-HIAA	NA
Apomorphine	15 min	101.6	89.7	99.9	98.6	86.8
1 mg/kg	30 min	147.3*	97.3	117.2*	68.5	92.1
	1 hr	95.1	69.0*	125.8*	91.0	102.2
	2 hr	66.9*	92.7	97.8	60.7*	95.1
Apomorphine	15 min	172*	45.5*	100.2	100.7	190.5*
10 mg/kg	30 min	118.2	60.8	93.1	127.4*	103.3
	1 hr	91.3	55.1*	94.9	93.4	85.1
	2 hr	95.1	27.5*	91.7	97.7	107.1
NPA	30 min	74.0*	52.8†	98.5	83.1†	95.1
0.1 mg/kg	1 hr	74.3*	75.3*	101.7	103.2	88.6
	2 hr	81.1	52.5†	98.0	107.1	105.9
	3 hr	61.8†	70.7*	98.5	111.4*	118.1
Ergocornine	30 min	100.4	45.1*	106.9	73.4*	98.3
2 mg/kg	1 hr	82.5	44.5*	96.0	61.1*	81.4*
	2 hr	110.9	37.4*	101.8	46.4*	98.5
	3 hr	118.7	42.7	89.3*	70.0*	91.5
Bromocryptine	30 min	99.9	80.5*	91.1	73 4*	95.2
10 mg/kg	1 hr	101.2	46.2†	90	77.4*	96.5
	2 hr	106.4	58.9*	93.8	91.9	109.3
	3 hr	90.4*	46.2†	90.1	94. 8	101.9
LSD	30 min	94.6	70.5	95.6	52.1†	103.3
9 mg/kg	1 hr	114.4	47.3†	98.6	71.8*	102.4
	2 hr	100.7	65.9*	87.0*	85.0*	139.9*
	3 hr	74.3†	67.5	86.0†	67.1†	100.6
Ergometrine	30 min	89.0	86.6	93.3	69.7†	
4 mg/kg	1 hr	89.8	77.4	93.2	65.2†	97.7
	2 hr	90.6	82.6*	96.6	72.4†	110.0
	3 hr	80.6†	67.5†	89.9	70.9†	98.7
Ergometrine	30 min	96.0	102.1	107.3	56.9†	91.3
10 mg/kg	1 hr	105.1	89.5	118.1	68.9†	93.1
	2 hr	121.7	86.4	112.2	70.8†	88.8
	3 hr	110.2	94.1	114.2	72.0†	89.0
Quipazine	1 hr	109.4	111.9	133.2†	83.7	99.5
50 mg/kg	2 hr	99.5	118.6	138†	77.7*	89.2
	4 hr	94.4	77.4*	114.9†	64.9†	84.9

Groups of mice were injected i.p. with drugs at the stated doses and exposed to auditory stimulation after the time shown. Mice were killed and cerebral amine and metabolite concentrations determined, as described in the "Methods" section. Results are expressed as percent of estimations in brains of control animals assayed concurrently. Significant changes compared to controls are denoted by: * $P < 0.05$, † $P < 0.01$. A line underneath a figure indicates where the standard error was >15 per cent of the mean.

Means (±SEM) of biochemical estimations in combined control (saline treated) mice were: DA, 576.2 ± 23.8 ng/g ($n = 42$); HVA 138.9 ± 8.6 ng/g ($n = 44$); 5HT 620.9 ± 13.9 ng/g ($n = 43$); 5HIAA 495.7 ± 23.3 ng/g ($n = 41$); NA 361.1 ± 11.6 ng/g ($n = 43$).

Estimations in brains of control mice not subjected to auditory stimulation revealed no significant differences in: DQ ($n = 20$); HVA ($n = 8$); 5HT ($n = 23$); 5HIAA ($n = 24$) or NA ($n = 33$) from the above.

contraversive rotation in unilaterally lesioned mice (NPA > apomorphine > LSD > ergometrine > ergocornine > bromocryptine [3].

The ratio of activity of NPA to apomorphine is the same against the two syndromes of reflex epilepsy (i.e. (±) NPA is 5 times more effective than apomorphine against myoclonic responses in *Papio papio*, whereas (−) NPA, the active isomer, is 10 times more effective than apomorphine against audiogenic seizures in DBA/2 mice). This ratio is less than that observed for stereotyped behaviour in the rat where (−) NPA is 35 times as potent as (−) apomorphine [13]. However, the complete failure of high doses of LSD or ergometrine (9 or 10 mg/kg) to block the initial "wild running" component of the audiogenic seizure response is in striking contrast with their ability to block initial myoclonic responses to photic stimulation in *Papio papio*. (Minimum effective doses in the baboon are: LSD, 0.05 mg/kg, and ergometrine, 1 mg/kg, compared with (±) NPA, 0.2 mg/kg, apomorphine, 1.0 mg/kg, and ergocornine, 1.0 mg/kg, and bromocryptine > 4 mg/kg [1, 14–16])

Part of the protective action of LSD (and probably ergometrine) in photosensitive baboons can be attributed to impairment of afferent transmission at the lateral geniculate [17]. Evidently LSD does not produce a comparable inhibition of afferent transmission in the auditory system of the mouse. Like apomorphine, LSD and ergometrine activate "desynchronise") the EEG in baboons, whereas egocornine and bromocryptine produce slowing in background rhythms [1, 16]. Clearly the receptor

Table 5. ED_{50} for blockade of clonic phase of audiogenic seizures in DBA/2 mice

	Interval (min)	ED_{50} mg salt/kg	ED_{50} μ moles/kg	References
(−)*n*-propylnorapomorphine	30	0.075	0.23	Anlezark, 1977*
Ergocornine	45	1.1	1.6	Anlezark *et al.*, 1976
Apomorphine	20	0.7	2.2	Anlezark *et al.*, 1976
Bromocryptine	60	5.0	6.7	Anlezark *et al.*, 1976
Ergometrine	30	9.7	22.1	Anlezark *et al.*, 1976†
Lysergic acid diethylamide	30	9.3	28.8	Anlezark *et al.*, 1976
Quipazine	120	50	152	(This paper)

The interval from intraperitoneal injection of drug to seizure testing was selected on the basis of the time of maximal behavioural effects. The ED_{50} was determined graphically (Anlezark and Meldrum, 1975).

* The ED_{50} for (−)*n*-propylnorapomorphine quoted here is higher than the value previously reported for (±)-*n*-propyl norapomorphine (Ashton *et al.*, 1976).

† The ED_{50} for ergometrine is a correction of the value stated by Anlezark *et al.*, 1976.

sites involved in the antiepileptic action in mice must be pharmacologically distinct from those producing EEG activation in baboons.

Monoamine metabolism

Apomorphine and n-*propylnorapomorphine.* An early increase in brain dopamine content after apomorphine has been described previously in rats, and attributed to an inhibition by apomorphine of monoamine oxidase, demonstrated *in vitro* [18]. Inhibition of monoamine oxidase could also explain the marked rise in NA seen early after apomorphine, 10 mg/kg. Obviously, inhibition of monoamine oxidase will not only increase brain DA and NA but will also reduce the rate of formation of HVA. The fall in HVA content 15 min after apomorphine 10 mg/kg is presumably a result of this. However, at no other times (and with no other drug) was a significant fall in HVA content observed synchronously with a significant increase in brain DA content, so that inhibition of the further metabolism of monoamines is unlikely to be the explanation for the majority of changes we observed.

The fall in cerebral HVA content observed after dopamine agonist drugs is generally attributed to a negative feedback mechanism, which may be either neuronal or biochemical. In the former case, following activation of the dopamine receptor, a change in the firing rate of the postsynaptic neurone, either directly or via interneurones, leads to a reduction in the firing rate of the dopaminergic neurone [19, 20].

In the latter case, activation of dopamine receptors on the cell bodies or dendrites of dopaminergic neurones ("autoreceptors" or "presynaptic receptors") leads to inhibition of tyrosine hydroxylase and a consequent decrease in the rate of DA synthesis [21]. This enzyme inhibition can explain the fall in DA content seen 30 min—3 hr after NPA, and at 2 hr after apomorphine, 1 mg/kg. Apparently, at this interval after the higher dose of apomorphine, direct inhibition of the further metabolism of DA largely compensates for the receptor-mediated inhibition of tyrosine hydroxylase, so that there is little net change in DA content. However, the two enzyme inhibitions (tyrosine hydroxylase and monoamine oxidase) act in consort to reduce the rate of synthesis of HVA so that its cerebral concentration falls to an exceptionally low level at this time.

It is clear from comparison of the time course of reduction in HVA content with the time course of changes in seizure responses, that the behaviour change is less sustained than the metabolic change. That this is also true for other behavioural effects attributed to dopamine agonist activation following apomorphine (e.g. stereotyped behaviour, or turning in unilaterally lesioned animals) is evident from comparison of the time course of such effects [22, 23] with our own and other accounts of the time course of changes in cerebral HVA [24]. Further, there are regional differences in the time course of changes in cerebral HVA; in the substantia nigra HVA remains normal or elevated during the period of maximal behavioural effects of apomorphine, whereas in the striatum a fall in HVA levels begins earlier [24]. Changes in the rate of formation of HVA due to changes in neuronal firing rate should occur simultaneously. The difference in the time course of the effects on seizures and on HVA content thus suggests that the reduction in HVA occurring relatively late after dopamine agonist administration is probably due to tyrosine hydroxylase inhibition following activation of DA autoreceptors.

Although both apomorphine and NPA exert effects on the cerebral content of the 5-HT metabolite, 5-HIAA, these are probably not due to direct actions on serotoninergic synapses, but to an indirect influence via their agonist action on DA receptors [25, 26].

Ergocornine and bromocryptine. Among the ergot alkaloids tested, ergocornine was the most potent at blocking the audiogenic seizure response. Although the time course of the fall in rectal temperature ran closely parallel to the decrease in the seizure response, as with apomorphine, the fall in cerebral HVA content reached its nadir later and was more prolonged. The most probable explanation is that the anti-seizure effect and the hypothermia are due to post-synaptic activation of DA receptors which shows some degree of tachyphylaxis—whereas the "autoreceptors" responsible for the decreased synthesis of DA show less tachyphylaxis.

The reduction in 5-HIAA content after ergocornine and bromocryptine is most probably an indication of diminished activity in serotoninergic neurones. Serotoninergic pathways from the nuclei of the median

raphe supply the basal ganglia; behavioural and biochemical experiments have provided evidence for interactions between the two systems [27–29]. However, the present evidence is not adequate to allow us to decide between changes in 5-HT turnover secondary to effects on dopaminergic receptors, changes due to activation on 5-HT receptors, or other alternatives.

LSD and ergometrine. The less marked hypothermia, and the later and smaller fall in HVA content after high doses of LSD and ergometrine, compared with ergocornine and bromocryptine, can be taken as indicative of a less potent dopamine agonist action. Turning in the unilaterally-lesioned rat is probably misleading in this respect. Activity within the serotoninergic neurones whose axons terminate within the basal ganglia decreases the turning produced by apomorphine or amphetamine [29]. Because of its action on serotoninergic "autoreceptors" LSD reduces the firing rate of sertoninergic neurones [30]. This has the effect of enhancing the dopamine agonist properties of the drug (at the dopaminergic synapses where this 5-HT-DA interaction occurs). The marked fall in cerebral 5-HIAA is, similarly, the consequence of the dramatic decrease in neuronal firing in the nuclei of the median raphe [30, 31].

Quipazine. Quipazine is a central 5-HT agonist [32] and the changes in 5-HT and 5-HIAA content observed are those expected of a serotonin agonist [33, 34]. The late decrease in cerebral HVA can be interpreted as secondary to the effect on serotoninergic pathways. The relative timing of the effects on 5-HIAA and HVA, and the absence of an effect on the wild running seizure response match the effects of ergometrine.

Hypothermia. Some dopamine agonist drugs have previously been shown to induce hypothermia in rats and mice [35–37]; and there is evidence from other pharmacological studies that a dopaminergic mechanism participates in the control of body temperature [37–40]. The similar time course and intensity of (a) the depression of body temperature, and (b) inhibition of the seizure response after apomorphine or the ergot alkaloids can thus be explained in terms of an agonist action at post-synaptic dopamine receptors in (a) the hypothalamus, and (b) other brain areas. However, the possibility must be considered that both effects arise from action at temperature-controlling neurones. A depression of audiogenic seizure responses is observed when body temperature is reduced by external cooling in the mouse [41]. However, the magnitude of the fall in body temperature required to prevent seizures (to below 29°) was greater than that observed here; the effect of rectal temperature in the range 29–35° was a prolongation of the latency of wild running. Nevertheless, apomorphine does not protect against audiogenic seizures when body temperature is slightly elevated by external heating. A more marked elevation of body temperature in mice can lower seizure threshold to the point where seizures occur spontaneously [42, 43]. The protection after apomorphine cannot be purely an effect of the lowered temperature because comparable protection is not seen in comparably cooled animals [41] and many drug treatments that produce comparable reductions in rectal temperature do not lead to protection against seizures (e.g. reserpine [44] and haloperidol [45]). A co-operative effect of a lowered body temperature and dopamine receptor activation appears to be responsible for the protection following apomorphine.

Part of the protective effect of ergot alkaloids appears to be temperature-dependent and part is clearly temperature-independent. As protection due to quipazine occurs in the absence of any change in temperature, it may be that the temperature-independent seizure protection after ergot alkaloids (including LSD) is due to serotonin agonist action.

A fall in body temperature could modify the magnitude of the changes in mono-amine metabolites. A focal decrease in the concentration of HVA is seen after focal injections of apomorphine into striatum and substantia nigra [24], when whole body temperature changes are unlikely to be significantly involved. The transport of acid metabolites from brain or CSF to blood could be slowed by a reduction in body temperature. This would have the effect of reducing the magnitude of decreases in HVA and 5-HIAA concentration, and thus explain the observation that the maximal decrease in HVA content occurs after the period of lowered rectal temperature.

Site of action: dopamine receptors. The primary site of "antiepileptic" action of apomorphine, NPA, ergocornine and bromocryptine is most probably a post-synaptic DA receptor. We have no direct anatomical evidence about which of the known DA receptor areas are involved. The fact that the protective action of apomorphine and of ergocornine can be blocked by pre-treatment with haloperidol (0.5 mg/kg [3] indicates that the receptors are pharmacologically of the type classified by [46] as DE receptors (i.e. excitation mediating). This is consistent with the weak effect of ergometrine (which is irritative at DE sites). An action within the basal ganglia can readily explain the failure of the seizure response to evolve after drug treatment. (The evolution of the successive stages of the response is known to depend on a complex interaction of motor output and sensory input with the seizure activity [47].) Complete failure of initiation of the seizure may require action at other sites influencing cortical activity or sensory input. The possibility of an effect on afferent pathways is indicated by evidence that sensory attention is modified by DA neurons [48].

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