EFFECTS OF APOMORPHINE, ERGOCORNINE AND PIRIBEDIL ON AUDIOGENIC SEIZURES IN DBA/2 MICE

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Audiogenic seizures in DBA/2 mice have been studied after administration of drugs believed to act as dopamine agonists. Apomorphine at 0.4 mg/kg delays all phases of the response, the tonic phase is absent after 2.0 mg/kg; the clonic phase is abolished by 10 mg/kg. Ergocornine (0.5-8.0 mg/kg) produces effects on the latency and occurrence of seizure stages similar to those of apomorphine. Piribedil, ET 495 (4-100 mg/kg) is less potent; even after 100 mg/kg clonic and tonic phases occurred in 50% of the mice.

Introduction Certain inbred strains of mice, when 20-32 days old, show a sequence of epileptic-like activity (wild-running, clonic jerks, tonic flexion then extension, terminating with respiratory arrest) if subjected to a loud noise of mixed spectral composition (Collins, 1972). Several studies (Lehmann, 1964; 1967; 1970) implicate monoaminergic systems in the induction or evolution of these 'audiogenic seizures'. In particular, (+)-amphetamine (15 mg/kg) diminishes the incidence or severity of seizures. Reserpine enhances audogenic seizures; this effect is antagonized by L-3,4-dihydroxyphenylalanine (200 mg/kg) (Boggan & Seiden, 1971). We have therefore tested the effect on audiogenic seizures of three compounds believed on the basis of various biochemical and behavioural tests to act as dopaminergic agonists in the rodent brain.

Methods DBA/2 mice (Fisons Pharmaceuticals Ltd), 23-28 days old, weighing 7-13 g, were placed under a dome, diameter 58 cm, and habituated for 30 seconds. Stimulation by an electric bell (Friedland Chimes, 3 inch diameter, producing 109 dB at mouse level) was applied for 60 s or until tonic extension occurred. The appearance of seizure stages was timed. Mice were pretreated with intraperitoneal injection of 0.9% w/v NaCl solution (saline) or of solutions containing apomorphine hydrochloride (Evans Medical), ergocornine hydrogen maleinate (Sandoz Ltd) or piribedil (ET 495, 1-3,4-methylenedioxybenzyl-4-(2-pyrimidinyl) piperazine-methane sulphonate) (Servier Laboratories).

Results Spontaneous exploratory motor activity was observed during habituation after saline and all drug doses. Sniffing and stereotyped head movements were prominent after the highest doses of apomorphine, piribedil and ergocornine. The latter drug at 8 mg/kg sometimes evoked tremors and retropulsion. All animals were capable of running, but after the highest doses of apomorphine and ergocornine the limbs tended to be rigidly extended and the back arched.

After saline pretreatment 'wild running' was invariably observed during auditory stimulation; later seizure stages were seen in 80-100% of mice. Latencies to onset of the successive phases (mean in s ± standard error) were: wild running, 0.8 ± 0.1 (n = 30); clonic, 8.0 ± 1.3 (n = 29); tonic, 11.1 ± 1.4 (n = 27); and respiratory arrest, 22.5 ± 1.8 (n = 26).

Figure 1a shows the effect of apomorphine (0.08-10.0 mg/kg) on the occurrence of the different seizure stages. The tonic phase was abolished by apomorphine, 2.0 mg/kg, and the clonic phase was absent after 10 mg/kg. The latency of wild running was increased at all doses, reaching 3.5 ± 1.1 s (n = 7) at apomorphine, 2.0 mg/kg. Latency of the clonic phase was doubled after apomorphine, 0.08-2.0 mg/kg.

The occurrence of seizure responses after ergocornine is shown in Figure 1b. The wild running phase was markedly delayed after 8.0 mg/kg (mean latency 3.7 ± 2.3 s, n = 8). The tonic phase was abolished after 2.0 mg/kg; the clonic phase was delayed after 2.0 mg/kg, and absent after 8.0 mg/kg.

Piribedil increased the latency of the wild running phase (e.g. 2.3 ± 0.4 s, n = 10, after 20 mg/kg; 3.9 ± 0.7 s, n = 8, after 100 mg/kg). Doses in the range 4-100 mg/kg tended to reduce the incidence of later stages of the seizure response. However after 100 mg/kg, 70% still showed a clonic phase and 50% a tonic phase, but the extensor component of the tonic phase was seen in only 30% and respiratory arrest in only 10%.

Discussion McKenzie & Soroko (1972) demonstrated that apomorphine (2.5-10.0 mg/kg) protected rats against maximal electroshock seizures, but that mice were not protected by apomorphine (2.5-160.0 mg/kg). Apomorphine also suppressed firing in a cobalt-induced focus in the rat (Dow, Hill & McQueen, 1974). However, it potentiated pentylenetetrazol convulsions in both mice and

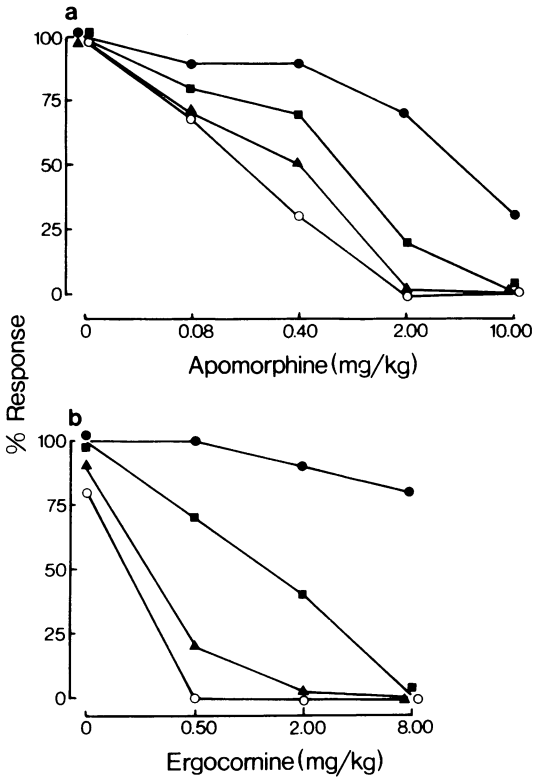

Figure 1 Graphs to indicate components of the seizure response to acoustic stimulation in DBA/2 mice. Five males and 5 females were tested after saline or each drug dose. The percentage showing the different seizure components is indicated as: (●) 'wild running', (■) clonic phase, (▲) tonic phase and (○) respiratory arrest. (a) Tests conducted 20 min after the intraperitoneal injection of saline or apomorphine hydrochloride (0.08-10.0 mg/kg). (b) Tests conducted 45 min after the intraperitoneal injection of ergocornine (0.5-8.0 mg/kg).

rats (Soroko & McKenzie, 1970). Our results demonstrate a powerful protective action of apomorphine (2.0-10.0 mg/kg) against audiogenic seizures in mice.

Evidence similar to that indicating a dopamine agonist action of apomorphine at receptor sites in the basal ganglia and elsewhere (Ernst, 1967; Anden, Rubenson, Fuxe & Hökfelt, 1967), has recently been produced for ergocornine (Fuxe, Corrodi, Hökfelt, Lidbrink & Ungerstedt, 1974), and for piribedil (Corrodi, Farnebo, Fuxe, Hamberger & Ungerstedt, 1972). However, the latter drug may owe its action on dopamine receptors to a metabolite (Miller & Iversen, 1974). Thus the strong anti-seizure effects of apomorphine and ergocornine (and the weaker effect of piribedil) and the similar effect of L-DOPA in reserpine-treated mice (Boggan & Seiden, 1971) may be a consequence of dopamine receptor activation. A role for dopaminergic systems in audiogenic seizures has yet to be defined, but there is evidence from several types of experiment that interaction between efferent and proprioceptive activity plays a part in the evolution of the seizure response.

The results with apomorphine, ergocornine and piribedil in DBA/2 mice are similar to those obtained in cobalt-induced epilepsy in the rat (Dow *et al.*, 1974). Thus the species difference between rats and mice observed for the anti-seizure effect of apomorphine (McKenzie & Soroko, 1972) appears to be a particular feature of tests using electroconvulsive shock. Although apomorphine and related drugs cannot be regarded as general anti-convulsants because of their lack of action against drug-induced seizures, a clear protective action has now been demonstrated in three very different rodent models of epilepsy.

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