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# Dopamine Agonists and Reflex Epilepsy

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Many studies indicate an involvement of cerebral norepinephrine and 5-hydroxytryptamine (5-HT) in experimentally induced seizures in animals (2,11,12), but a critical role for dopamine (DA) has not been emphasized. Some evidence is available to show that DA may modify experimental seizures. L-Dihydroxyphenylalanine (L-DOPA) reverses reserpine-induced enhancement of audiogenic seizures (4), and apomorphine raises the maximal electroshock seizure threshold in rats (13). We have tested drugs believed to act as agonists at central DA receptors in two models of reflex epilepsy: sound-induced (audiogenic) seizures in DBA/2 mice and photically induced seizures in the Senegalese baboon *Papio papio*. In DBA/2 mice, the relation between the time course of action of drugs against audiogenic seizures and their effects on the cerebral metabolism of DA and 5-HT [estimated by whole brain concentrations of their metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA)] was examined.

The drugs used were the DA agonists n-*N*-propylnorapomorphine (NPA) and apomorphine, the ergot alkaloids ergocornine, bromocryptine (CB 154, 2-bromo-$\alpha$-ergocryptine), ergometrine, and lysergic acid diethylamide (LSD), and the 5-HT agonist quipazine [2-(1-piperazinyl)-quinoline maleate]. These ergot alkaloids possess DA agonist properties in behavioral and biochemical tests (3,7,8,11,14) and interact with central 5-HT receptors (1,5). Quipazine acts directly on 5-HT receptors with only indirect effects on DA neurons (6,15).

## AUDIOGENIC SEIZURES IN DBA/2 MICE

Groups of 10 DBA/2 mice (19 to 23 days old) were subjected to auditory stimulation (doorbell, 109 dB at mouse level) following intraperitoneal injection of drugs at the doses and times shown (Fig. 1). In preliminary experiments, the dose-response relations and $ED_{50}$'s (clonic phase) were determined for each drug, and all gave dose-related protection against seizures (2,3). The doses chosen were related to the $ED_{50}$'s and the order of potency was ($ED_{50}$'s in mg/kg in parentheses): NPA (0.1) > ergocornine (1) = apomorphine (1) > bromocryptine (5) > LSD (9) $\geqslant$ ergometrine (10)

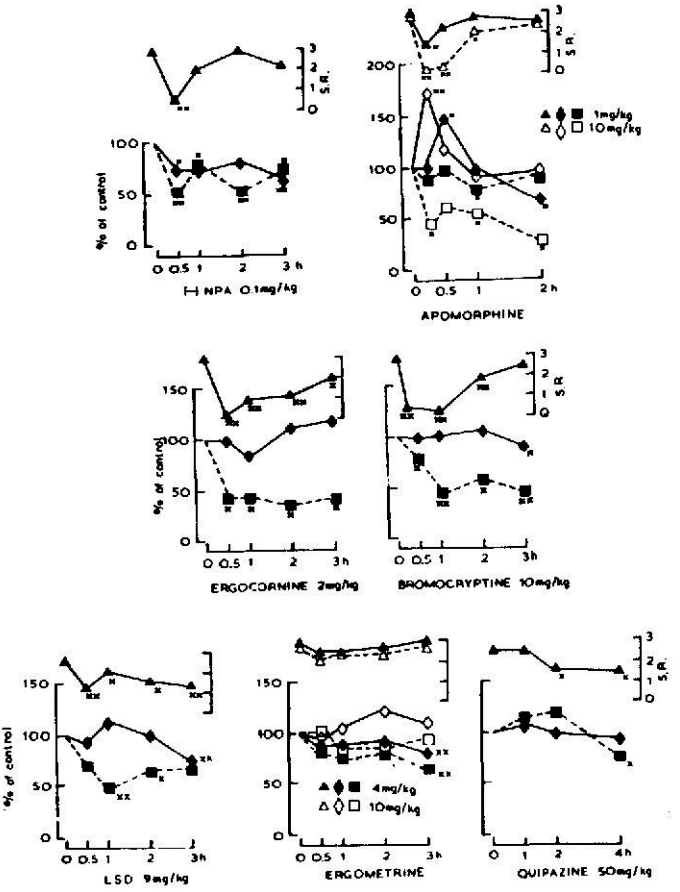


FIG. 1. Effects of (−)n-N-propylnorapomorphine (NPA), apomorphine, ergot alkaloids, and quipazine on audiogenic seizure response (S.R.) and whole brain concentrations of dopamine (DA) and homovanillic acid (HVA) in 19–23-day-old DBA/2 mice. S.R. ▲: right-hand axis, upper part of each diagram, graded as follows: O = no response; 1 = wild running; 2 = clonus; 3 = hindlimb tonus. Each point represents the mean maximum S.R. for 10 animals. Significant differences ($p < 0.05$) from control (Fisher's exact probability test) are denoted: x, incidence of tonic phase different from control; xx, incidence of clonic phase different from control. Biochemical measurements: ◆ DA; ■ HVA, left-hand axis, lower part of each diagram. Results are expressed as % of estimations in concurrent control animals treated with vehicle and exposed to auditory stimulation. Each point represents the mean of 5 determinations. Significant differences from control (Student's *t*-test) are denoted: x $p < 0.05$; xx $p < 0.01$. Time in hours on the lower axis.

> quipazine (50). Maximum seizure response for each mouse was recorded (see Fig. 1 legend). Mice were killed by decapitation after 60 sec of stimulation or during tonic extension. Estimations of whole brain concentrations of DA, 5-HT, HVA, and 5-HIAA were made as previously described (10).

The time course of changes in seizure susceptibility and DA metabolism is shown in Fig. 1. NPA reduced seizure response and cerebral concentrations of DA and HVA. Apomorphine (1 mg/kg) had a transient protective

effect against seizures and reduced HVA whereas DA rose briefly. More profound and longer lasting effects occurred following 10 mg/kg. Ergocornine and bromocryptine reduced seizure response for 2 to 3 hr and induced profound decreases in HVA with little change in DA. LSD also reduced seizure response and HVA for 3 hr, but at a high dose. Quipazine diminished seizure response and HVA with a long latency of onset. DA concentrations were unchanged. The failure of ergometrine to influence seizure susceptibility and its weak action on DA metabolism were unexpected in view of its previously determined ability to protect against audiogenic seizures and DA agonist properties in behavioral tests.

## PHOTICALLY INDUCED SEIZURES IN BABOONS

The experiments were performed on 11 adolescent Senegalese baboons. Stroboscopic stimulation (Dawe Strobotorch model 1202D, 15 to 35 flashes/sec) was applied in 5-min tests before and 0.25 to 5.5 hr, at hourly intervals, after intravenous drug administration. Myoclonic responses were graded: 0 = no response; 1 = eyelid myoclonus; 2 = myoclonus of head, neck, and upper limbs; 3 = whole body myoclonus; 4 = myoclonus continuing after termination of stimulation; S = generalized tonic-clonic seizure. Baboons varied in their responses, but most showed grade 2 or 3 in control tests. The drugs used were: (±) NPA, apomorphine, ergocornine, ergometrine, and bromocryptine. LSD (0.04 to 0.4 mg/kg) had already been shown to potently diminish photically induced myoclonus in baboons (17) so this was not repeated.

### NPA and Apomorphine

Apomorphine (1 mg/kg) abolished myoclonic responses to photic stimulation 15 min after administration. Control responsiveness returned after 1 to 2 hr. (±) NPA (0.05 to 0.2 mg/kg) reduced responses for up to 4 hr.

### Ergot Alkaloids

Ergometrine (0.15 to 1 mg/kg) was the most effective of the three ergot alkaloids and abolished or reduced myoclonic responses for 1 to 2 hr. Ergocornine (0.5 to 2 mg/kg) had a longer time course of action, photically induced responses being reduced or absent for up to 3 hr, but was more toxic inducing sedation and large-amplitude slow waves on the EEG. Bromocryptine (0.5 to 4 mg/kg) had a weak action against myoclonic responses, but this had prolonged time course with responsiveness slightly reduced for up to 6 hr following the higher doses.

The order of potency of these drugs, based on the dose giving a consistent reduction in myoclonic responsiveness, was: LSD $\geqslant$ NPA $>$ ergometrine $>$ apomorphine = ergocornine $>$ bromocryptine.

## COMPARISON OF DRUG ACTIONS IN MICE AND BABOONS

Comparing the orders of potency of drugs to reduce seizure activity in mice and baboons, it can be seen that apomorphine and ergocornine are as potent as each other in both models. NPA is more effective and bromocryptine less effective than either. However, both LSD and ergometrine are more effective in reducing photically induced myoclonus than in altering audiogenic seizure susceptibility. Obviously, different anatomical pathways are involved in the mediation of seizure activity in each model, and the dependence in the baboon on transmission in the visual pathway may explain the differing potencies of the two ergot alkaloids. The ergot alkaloids differ in their abilities to interact with central 5-HT neurons as assessed by their action on cerebral concentrations of 5-HIAA in DBA/2 mice. They all reduced cerebral 5-HIAA. Ergocornine (2 mg/kg) and bromocryptine (10 mg/kg) had a longer-lasting and more profound effect on HVA than on 5-HIAA (maximal decreases in 5-HIAA 46% of control after 2 hr and 73% of control after 0.5 hr, respectively). LSD (9 mg/kg) was almost equally effective in reducing cerebral 5-HT metabolism as in reducing DA turnover, whereas ergometrine (4 and 10 mg/kg) significantly diminished cerebral 5-HIAA at all times after administration (maxima: 4 mg/kg, 65% of control after 1 hr; 10 mg/kg, 57% of control after 0.5 hr) in contrast to its weak action on DA metabolism.

In neurophysiological experiments, LSD potently inhibits the firing rate of 5-HT neurons in the lateral geniculate body (9), a relay in the visual pathway. In photosensitive baboons, the drug modifies visual evoked responses in the lateral geniculate body, and this correlates well with the reduction in photosensitivity (16). A similar mechanism may operate for ergometrine as it is structurally similar to LSD. The results presented here strongly suggest that drugs which interact with central 5-HT receptors are potent inhibitors of reflex epilepsy in the baboon. DA agonist action is also effective as shown by the reduction in myoclonic responses following NPA and apomorphine. In DBA/2 mice, the potency of NPA, apomorphine, and the ergot alkaloids to reduce audiogenic seizures is similar to their potencies in behavioral tests of central DA function (3). Thus, DA agonist action is probably the mechanism by which these drugs reduce audiogenic seizure susceptibility. This is supported by the finding that the protective effects of ergocornine and apomorphine are blocked by the DA antagonist haloperidol (3), and that ergometrine which had little effect on DA metabolism was ineffective in

reducing audiogenic seizures. However, a central 5-HT agonist action of ergot alkaloids in protection against audiogenic seizures cannot be excluded.

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