EFFECT OF NOMIFENSINE ON BRAIN AMINES AND EPILEPSY IN PHOTOSENSITIVE BABOONS

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1 The literature, both clinical and experimental, suggests that tricyclic antidepressants are potentially epileptogenic. Using the experimental model of epilepsy provided by the photosensitive baboon, *Papio papio*, the epileptic potential of four antidepressant drugs, two of which are tricyclic, has been assessed. The drugs used were imipramine 1, 10 and 20 mg/kg, chlorimipramine 1, 10 and 20 mg/kg, maprotiline 1 and 10 mg/kg and nomifensine 10 and 20 mg/kg. In a second series of experiments the 5-hydroxytryptamine (5-HT) precursor 5-hydroxytryptophan (5-HTP) 10 and 25 mg/kg has been administered before administration of imipramine 10 mg/kg and chlorimipramine 10 mg/kg.

2 The results of the experiments indicate that at 10 mg/kg imipramine, chlorimipramine and maprotiline all induce seizures and lower the seizure threshold. In contrast nomifensine at this dose did not alter the seizure threshold. 5-HTP 25 mg/kg administered before the antidepressants, abolished seizures. These results are discussed in the light of other experiments which have attempted to explain the pathophysiology of epileptic seizures following antidepressants, and it is concluded that dopaminergic mechanisms are probably responsible for the differing effect noted with nomifensine.

Introduction

Since the first tricyclic antidepressants came into use in the late 1950s there have been reports in the literature of their ability to precipitate epileptic seizures. One report, summarizing experience with these drugs in 1962, suggests that "from the increasing number of reports in the literature from intoxication from overdose of imipramine it seems that the major consistent findings are convulsions" (Garrison & Moffitt, 1962). These earlier authors reported their findings following overdose of tricyclic antidepressants, and suggested that they were more likely to occur in patients with previous neurological damage (Steel *et al.*, 1967; Brooke & Weatherly, 1959). As more clinical trials were published, however, there were more reports of seizures occurring at normal therapeutic levels, in one series the incidence being 3–4% (Brown *et al.*, 1973). These clinical reports have been supported by investigations in the laboratory. Several authors have shown that tricyclic antidepressants induce EEG spike-like activity, or induce EEG seizures (Van Meter *et al.*, 1959; Steiner & Himwich, 1963). With the development of other antidepressants, many of which do not have tricyclic structure, the possibility arose that some such antidepressants may have less effect on the seizure threshold. Although the pathogenesis of the tricyclic-induced seizures is not known, it has been suggested that the epileptogenic effects are a consequence of increased serotonergic activity (Westheimer &

Klaywans, 1974). Thus, using guinea-pigs, it has been observed that large doses of 5-HTP induced 'myoclonic' seizures in guinea-pigs, but that lower doses (100–200 mg/kg) would not produce such seizures unless combined with imipramine. The experiments to be described were designed to test further the hypothesis that different antidepressants may differ in their ability to lower the seizure threshold, and to examine further the relationship of the convulsant effect to brain monoamines.

Methods

Ten adolescent baboons from the Casamance region of Senegal showing the property of photosensitive epilepsy were used (Meldrum *et al.*, 1975a). The animals weighed between 3.5 and 7.5 kg, and for the purposes of EEG recording were implanted with epidural silver–silver chloride skull electrodes. These electrodes were held in place by acrylic resin fixed to the calvarium. The EEG was recorded by connecting the electrodes to a Galileo SLE 17-Channel EEG machine.

To test the myoclonic responsiveness of the animals to intermittent light stimulation (ILS), the animals are initially transferred from their cage to a primate chair. In static conditions of illumination a Dawe Strobotorch (model 1202D) was then held 15–20 cm

from the eyes of the animals, and flashed at a rate of 15–35 flashes per second. In all the experiments each individual 'test' with ILS lasted 5 min, unless the animal was observed to have a full tonic-clonic seizure, in which case the test was terminated. Four antidepressants were used and their ability to alter the seizure threshold recorded. In a subsequent experiment two tricyclic antidepressants were administered subsequent to L-5-HTP. When the antidepressants were given alone the testing was carried out at 0.25 h, at 1 h, and then hourly for 5 h after drug administration. When the amino acid precursor was given with the antidepressant, testing was carried out before any injection, 0.25 and 1.5 h after injection of 5-HTP, and then at 0.25, 1, 2, and 3 h following administration of antidepressant. During any individual test, the photically induced myoclonic responses were scored on a scale from 1–5 (see Figure 2).

Drugs used in the experiments were as follows: imipramine (Tofranil), chlorimipramine (Anafranil), maprotiline (Ludiomil), and nomifensine (8-amino, 2-methyl, 4-phenyl, 1-2-3-4-tetrahydroisoquinoline hydrogen maleate), at doses from 1–20 mg/kg. Where 5-HTP was used, it was given at a dose of 10 or 25 mg/kg, and subsequently chlorimipramine or imipramine was given at a dose of 10 mg/kg.

Saline experiments were carried out for comparison. No animal received more than one experiment per week. In analyzing the results for experiments comparing individual antidepressants the scores which the animal obtained following various doses of antidepressants were compared with the animal saline scores. Assessments were made over a whole 6 h testing period. In view of the fact that the major changes occur within the first hour statistical analysis were carried out on the results only after the first hour. The results of the first two tests were summated, and comparison made with the saline results for the same period. Statistical analysis used the Mann-Whitney U Test (Siegel, 1956).

Results

All animals showed some photomyoclonic responsiveness to ILS. Following saline, results varied from minimal eyelid myoclonus to full tonic-clonic seizure; five of the ten animals produced stable responses throughout all the 6 h of recording. Overall there was a tendency for scores at the end of the day to be lower than at the beginning of the day, but this was only a small decline in responsiveness. One animal had a full tonic-clonic seizure in response to ILS after receiving saline.

Figure 1 Comparison of effects on myoclonic responses to photic stimulation in the first hour after treatment with antidepressants (10 mg/kg i.v.). Nomifensine compared with imipramine, $P < 0.05$; nomifensine compared with maprotiline, $P < 0.02$; nomifensine compared with chlorimipramine, $P < 0.001$; chlorimipramine, maprotiline, imipramine, not significant.

Imipramine

Two animals received imipramine 1 mg/kg and results were not different from saline. Six animals received imipramine 10 mg/kg, and five showed enhanced responsiveness at 0.25 and 1 h (Figure 1). All five had a full tonic-clonic seizure at 0.25 hours. Again there was a tendency for scores to be lower at the end of the 6 h but one animal had increased myoclonic responsiveness for the whole of 6 h. After imipramine 20 mg/kg, all three animals had a spontaneous seizure before ILS and two out of three had a second seizure during ILS at 1 hour.

Chlorimipramine

Two animals received chlorimipramine 1 mg/kg and no change was observed in seizure activity compared with the saline results. Four animals received chlorimipramine 10 mg/kg (see Figures 1 and 2). Two of these animals had a seizure within the first hour in response to ILS. From 2–6 h, there was a tendency for diminished responsiveness, as had been observed with

Figure 2 Change in myoclonic responses to photic stimulation in *Papio papio* after administration (at time zero) of saline (●) or of 5-HTP 10 mg/kg (▲) or 25 mg/kg (●) followed 2.25 h later by chlorimipramine 10 mg/kg. Myoclonic responses to photic stimulation scored 1-5 as follows: 1, myoclonus of eyelids; 2, myoclonus of face and neck; 3, myoclonus of all limbs; 4, myoclonus continuing beyond the end of photic stimulation; 5, tonic-clonic seizure with postictal 'silence'.

saline. Three animals received chlorimipramine 20 mg/kg and all three had a seizure at 15 minutes. Two out of three had a spontaneous seizure before ILS.

Maprotiline

Two animals received maprotiline 1 mg/kg. No change was observed in the animals' responsiveness compared with saline results. Five animals received maprotiline 10 mg/kg; one animal died following injection. Of the remaining four, one animal had a seizure at 15 min, and two animals showed increased responsiveness when compared with the relevant saline results. From 2-6 h, an inconsistent pattern was seen, with either an increase or a decrease over the saline results being observed.

Nomifensine

Five animals received nomifensine 10 mg/kg. One animal died 2 h after injection. None of the five animals was observed to have a seizure following this dose of nomifensine. Four out of the five animals showed diminished myoclonic responsiveness during the first hour compared with saline results, and the only

animal to have had a seizure on saline showed a markedly diminished score at 15 minutes. In the four animals tested from 2-6 hours, results were similar to those for saline. Three animals received nomifensine 20 mg/kg. One had a spontaneous seizure before ILS, one had a seizure during ILS, and one was unresponsive throughout testing, although that animal had responded with saline.

EEG and behavioural changes during the experiments

The most marked changes were seen following imipramine and chlorimipramine. There was significant slowing of the background rhythm and isolated spikes were observed with a background of theta and delta activity. These changes seemed to occur within 5 min of injection and lasted from 2-3 hours. They were most prominent after 20 mg/kg, less changes being observed after 10 mg/kg, and no changes after 1 mg/kg. Nomifensine was in contrast to the above in that there was decline in the slow background rhythm of the EEG, and the animals were seen to be much more alert with less spontaneous drowsiness. Some of the animals on nomifensine were noted to become excited, emitting cries and seeming restless. Pilo-erection was observed as was increased salivation. No alteration was observed in the amount of spike-wave activity on the EEG, and sustained fast activity was recorded in contrast to periods of slow-wave activity observed following imipramine and chlorimipramine. No consistent behaviour or EEG changes observed following maprotiline.

5-HTP

In another experiment, saline or 5-HTP 10 mg/kg or 25 mg/kg were given before administration of imipramine 10 mg/kg and chlorimipramine 10 mg/kg. Tonic-clonic seizures were observed within 1 h of giving both antidepressants following the administration of saline. With 5-HTP 10 mg/kg a decline in myoclonic responsiveness was noted between the 90 min before injection of the antidepressant, compared with the saline control. With the addition of the tricyclic drug, however, full tonic-clonic seizure activity was observed within one hour. Following 5-HTP 25 mg/kg, myoclonic responsiveness diminished compared with controls for up to 90 min, and following the administration of the antidepressants the myoclonic responsiveness remained diminished. In three out of four tests no responsiveness was observed following the antidepressant for up to 3 h (see Figure 2).

Discussion

Our results have shown that four different antidepressants, all of the non-MAO inhibitor variety,

which differ in their ability to block the re-uptake of various brain monoamines, differ also in their potential to lower the seizure threshold. Thus, at 10 mg/kg, chlorimipramine and imipramine and maprotiline all induced epileptic seizures or lowered the seizure threshold of the animals. In contrast, nomifensine at this dose did not induce seizure activity and indeed in some of the animals seemed to protect against seizures (see Figure 1).

The results with chlorimipramine and imipramine are in accordance with the clinical reports mentioned in the introduction. There are some clinical reports of seizures following maprotiline (Jacobs & Hutchinson, 1974) so our results for this drug are also in accordance with the clinical situation.

The results with nomifensine stand in contrast to the other antidepressants. It is germane to consider why this may be so. Although Westheimer & Klaywans (1974) have suggested that the epileptogenic potential of the tricyclic drugs is related to their ability to block the re-uptake of 5-HT, the results of our experiments do not support this. Thus, it is known that chlorimipramine is five times more powerful than imipramine in its ability to influence 5-HT re-uptake (Horn & Trace, 1974). In these experiments they are shown to be equally epileptogenic. Similarly maprotiline is reported not to alter the re-uptake of 5-HT, but to be more specific for its effect on catecholamine re-uptake (Maître *et al.*, 1975), but this too promotes seizures.

Finally, the inhibition of the myoclonic responses following 5-HTP 25 mg/kg before administration of the antidepressant, an effect not observed after administration of saline or 5-HTP 10 mg/kg, strongly suggests that the enhancement of serotonergic transmission is not responsible for the production of the seizures. The hypothesis is advanced that the different effect of nomifensine is due to its effect on monoamines other than 5-HT.

Although it has been reported that nomifensine is powerful in blocking the re-uptake of NA (Schact & Heptner, 1974), it also seems to be particularly potent in blocking the re-uptake of DA. Generally, tricyclic antidepressants have a low affinity for dopamine receptors, probably related to their aromatic ring constraint and a rigid dihedral angle (Horn *et al.*, 1971). Nomifensine is said to act "after the disruption of presynaptic events", and the suggestion has been made that it "resembles apomorphine, a direct receptor activating agent" (Costall *et al.*, 1975).

This difference between nomifensine and the other drugs tested may be relevant to the differing action on the seizure threshold. Thus, it has been shown previously using the photosensitive baboon that DA agonists including apomorphine are anti-epileptic, whereas DA antagonists are epileptogenic (Meldrum *et al.*, 1975b). Nomifensine, therefore, by virtue of its inherent DA agonist activity, may alter the seizure threshold and protect animals from seizures.

Evidence for its inherent dopaminergic potential is further supported by the behavioural changes and EEG changes observed in these experiments following nomifensine, which are in marked contrast to the changes observed following imipramine and chlorimipramine. Thus, the restlessness, pilo-erection, salivation, and sustained fast activity on the EEG were similar to changes reported in the same animal model following the administration of DA agonists such as apomorphine (Meldrum *et al.*, 1975b).

The experiments reported here are less conclusive following 20 mg/kg of imipramine, chlorimipramine and nomifensine. Even at that dose, however, it is clear that the response observed following nomifensine was different from the other two drugs.

These experiments suggest that not all antidepressants that block the re-uptake of brain monoamines will necessarily lower seizure threshold. Clinically, this has important implications. If new antidepressants are to be introduced, it is important that they have less side-effects than existing ones. Epileptic seizures are one of the more severe side-effects of tricyclic antidepressants, and the development of antidepressants that do not possess seizurogenic potential is to be welcomed. An additional use for such drugs will be found in the management of depressed epileptic patients. Thus, it is known that depression is the commonest single psychiatric symptom in epileptics, and to treat depression in such patients the use of drugs possessing convulsant potential is illogical and inappropriate. A drug which was both antidepressant and anticonvulsant would therefore be most useful in their clinical management.

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Discussion

PROFESSOR TURNER (Chairman) commented that he was surprised that Dr Costall, having demonstrated that α -methyl-*p*-tyrosine plus reserpine, completely abolished the action of nomifensine, still suggested that nomifensine had some direct agonist activity of its own.

DR COSTALL (Bradford) replied that nomifensine was very resistant, relative to amphetamine, to neuroleptic blockade and it was for this reason that possible postsynaptic activity was suggested. She commented that, as Professor Marsden had indicated, there are many experiments which could be designed to elucidate this but that they would be very time consuming.

DR NAYLOR (Bradford) commented that Dr Schact's (Frankfurt) evidence indicated that nomifensine does not cause *release* of either NA or more particularly DA, and that one is left in a quandary as to how the drug works. He wondered about the effects of nomifensine on 5-HT. The behavioural effects of nomifensine are abolished by pretreatment with reserpine plus α -methyl-*p*-tyrosine, a finding confirmed in at least three independent laboratories. Reserpine is, however, a relatively crude pharmacological tool: it depletes not only NA and DA but also 5-HT and significantly modifies cholinergic mechanisms.

DR NAYLOR wondered whether some of the behavioural effects that he and Dr Costall had observed were due to release, augmentation or some other manipulation of 5-HT mechanisms within the brain. He noted that Dr Costall had shown that one of the behavioural effects of nomifensine was very convincingly modified by a brain lesion which selectively depleted cerebral 5-HT.

DR NAYLOR further commented on the considerable data demonstrating that nomifensine is a potent inhibitor of catecholamine uptake. Other drugs, such as bengtropine, are also effective in blocking DA uptake but they do not induce the behavioural syndrome or spectrum of activity produced by nomifensine.

DR WOODRUFF (Southampton) commented that he and his colleagues had also been investigating whether nomifensine has a direct effect on receptors. He had used a DA-sensitive adenylate cyclase, which is believed to be a very good model for DA receptor activity, and found no effect whatsoever with nomifensine or its M_2 metabolite. He wondered whether there was another active metabolite, possibly a dihydroxy analogue of nomifensine, since previous work has shown that most compounds which have a direct effect on DA receptors have two hydroxyl groups in the molecule.