Cortical stimulation in rabbits by fenfluramine is probably due to an unusual metabolite

Having worked with fenfluramine in several species of laboratory animals (but not rabbits) for several years (Foxwell, Funderburk & Ward, 1969) we were surprised by the report of Mayer, Southgate & Wilson (1970) who found that rabbits showed an alert pattern in their cortical EEG tracings after the intravenous administration of equianorectic doses of (+)-amphetamine sulphate (2 mg/kg) or fenfluramine hydrochloride (8 mg/kg). In other experiments the EEG derived from the cortex was slowed by prior administration of pentobarbitone and then "both anorectic drugs showed a clear-cut alerting action."

We have examined the effects of fenfluramine at several levels of the neuraxis in cats with chronically implanted stainless steel electrodes. These results were compared with those obtained in identical experiments with (+)-amphetamine.

Unlike (+)-amphetamine, fenfluramine slowed cortical electrical waves, blocked cortical after-discharges and reduced the effects of stimulating the ascending activating system. Like (+)-amphetamine, fenfluramine reduced thalamic recruitment and increased the electrical activity in the ventromedial nucleus of the hypothalamus without modifying the activity of the lateral hypothalamus.

Similar results were obtained in recent experiments on cats designed after the methods of Mayer & others (1970). Cortical waves, slowed by pentobarbitone, were speeded with (+)-amphetamine and slowed further by fenfluramine. We have never observed an alerting response in the tracing of a cat after administration of fenfluramine. Large, lethal doses of fenfluramine do not produce convulsions in the cats; rather, the cortex becomes isoelectric just before the heart stops beating.

We have now repeated similar experiments in rabbits and found entirely different results. As reported by Mayer & others (1970), fenfluramine speeded the cortical waves slowed by pentobarbitone very much the same as did (+)-amphetamine.

Recent unpublished studies by Chandler, Dannenburg, Polan & Thompson offer a possible explanation for these divergent results. These observers studied the metabolites of fenfluramine in calves and found de-ethylated fenfluramine (norfenfluramine) to be a major metabolite. Furthermore, fenfluramine appeared to produce CNS stimulation in the calves. Norfenfluramine produces CNS stimulation in mice similar to that produced by (+)-amphetamine. If rabbits metabolize fenfluramine much as calves do, and accumulate norfenfluramine, this would account for the stimulant action of fenfluramine in rabbits.

It is premature, however, to translate this stimulant effect of fenfluramine in rabbits to man as proposed by Mayer & others because Bruce & Maynard (1968) have shown that norfenfluramine is not a major metabolite of fenfluramine in man.

A few cases of CNS stimulation by large overdoses of fenfluramine in man have been reported (see Mayer & others, 1970). It appears possible that this could result from the small amount of norfenfluramine (3%) that is formed from the parent drug or from abnormal metabolism. A report by Richards (1969) suggests that the latter possibility occurs.

Department of Pharmacology,
A. H. Robins Company,
1211 *Sherwood Avenue,*
Richmond, Virginia 23220,
U.S.A.

WILLIAM H. FUNDERBURK
JOHN W. WARD

May 19, 1970

REFERENCES

BRUCE, R. B. & MAYNARD, W. R., Jr. (1968). *J. pharm. Sci.*, **57**, 1173–1176.
FOXWELL, M. H., FUNDERBURK, W. H. & WARD, J. W. (1969). *J. Pharmac. exp. Ther.*, **165**, 60–70.
MAYER, S. R., SOUTHGATE, P. J. & WILSON, A. B. (1970). *J. Pharm. Pharmac.*, **22**, 239–240.
RICHARDS, A. J. (1969). *Lancet*, **2**, 1367.

Adrenergic neuron blocking action of dehydroemetine

In recent years, dehydroemetine appears to have replaced emetine in the treatment of amoebiasis. Dehydroemetine is less toxic than emetine, but like emetine, it produces a fall in blood pressure (see *Extra Pharmacopoeia* 1967). The hypotensive effect of emetine has been ascribed to the interference in the release of noradrenaline at the adrenergic nerve endings (Ng, 1966a; 1966b; Abraham, 1968). It is possible that a similar action may be shared by dehydroemetine.

To investigate the effect of dehydroemetine on adrenergic transmission, observations were made on Finkleman (1930) preparations of the rabbit ileum. Preparations were suspended in 50 ml of McEwen solution maintained at 35° and equilibrated with a gas mixture of 5% carbon dioxide in oxygen. The periarterial sympathetic nerves were stimulated through a bipolar electrode (Burn & Rand, 1960) with supramaximal shocks (10–20 V) of 0·5 ms at 20 to 50 Hz for 20 to 30 s. The movements of the preparations were recorded on a kymograph by an isotonic lever.

Segments of intestine removed from six rabbits all showed spontaneous pendular movements. They were inhibited by noradrenaline (0·05–0·1 μg/ml) or by electrical stimulation of the perivascular nerves. Hexamethonium (50–100 μg/ml) did not abolish the inhibitory response produced by nerve stimulation. It was therefore concluded that the electrical stimuli were applied to post-ganglionic adrenergic nerves. Addition of dehydroemetine dihydrochloride (2–10 μg/ml) to the organ bath did not affect the spontaneous activity of the rabbit ileum. On the other hand, dehydroemetine initially reduced and subsequently abolished the inhibitory effect of nerve stimulation. When the effect of nerve stimulation was abolished by dehydroemetine, added noradrenaline still inhibited the spontaneous movements of the rabbit ileum.

These results show that dehydroemetine has no blocking action on the direct effect of noradrenaline on the rabbit ileum. Blockade of the inhibitory effects of nerve stimulation suggests that the action of dehydroemetine is on the adrenergic nerve endings. This pharmacological property is therefore qualitatively similar to the adrenergic neuron blocking action of emetine (Ng, 1966a, 1966b; Abraham, 1968).

We wish to thank La Roche & Co. Ltd. for the gift of dehydroemetine dihydrochloride.

Department of Pharmacology,
University of Singapore,
Singapore, 3.

K. K. F. NG
Y. T. NG

May 16, 1970

REFERENCES

ABRAHAM, G. J. S. (1968). *Indian J. med. Res.*, **56**, 431–427.
BURN, J. H. & RAND, M. J. (1960). *J. Physiol., Lond.*, **150**, 295–305.
Extra Pharmacopoeia, (1967) 25th edn. p. 579, London: The Pharmaceutical Press.
FINKLEMAN, B. (1930). *Ibid.*, **70**, 145–157.
NG, K. K. F. (1966a). *J. Pharm. Pharmac.*, **18**, 255–256.
NG, K. K. F. (1966b). *Br. J. Pharmac. Chemother.*, **28**, 228–237.