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Species-dependent effects of fenfluramine on the central nervous system

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The cortical effects of fenfluramine and a metabolite, norfenfluramine, were studied in rabbits and cats. The parent compound produced slow waves in the e.e.g. which were compatible with sedation in cats. Norfenfluramine also produced slow waves and apparent sedation in cats, but neither compound produced marked changes in the cortical waves of rabbits. When cortical waves in both species were slowed with pentobarbitone, fenfluramine increased the frequency of the waves in rabbits but did not alter the frequency in cats. Both fenfluramine and the metabolite blocked cortical afterdischarges in both species. There is no apparent explanation for the differences in the action of the two drugs in the two species.

Fenfluramine, an anorectic agent, is related structurally to amphetamine but it has been shown to be without cortical stimulant action in most experimental animals and in man (Colmore & Moore, 1966; Le Douarec, Schmitt & Laubie, 1966; Hill & Turner, 1967; Ziance & Kinnard, 1967; Foxwell, Funderburk & Ward, 1969) and it occasionally produces drowsiness in man (Duncan, Hyde & others, 1965; Traherne, 1965). Fink & Shapiro (1969) found that in man fenfluramine produced e.e.g. patterns that resembled those produced by 50 mg of amobarbitone but were unlike those produced by (+)-amphetamine. The lack of stimulant action of fenfluramine, however, has been questioned. Jesperson, Bonaccorsi & Garattini (1969) have shown that it causes hyperthermia and signs of central nervous system excitation in mice treated with a combination of dopa and pheniprazine. Large overdosages in man have also resulted in convulsions (Riley, Corson & others, 1969; Campbell & Moore, 1969; and others). More recently Mayer, Southgate & Wilson (1970) reported that fenfluramine produced cortical stimulation in rabbits and this has since been confirmed (Funderburk & Ward, 1970). Since this finding contrasts sharply with the finding that fenfluramine slowed cortical waves in cats and produced other signs of sedative action in this species (Foxwell & others, 1969), the present study was undertaken to compare the actions of fenfluramine and its de-ethylated metabolite, norfenfluramine (Bruce & Maynard, 1968), in rabbits and in cats.

METHODS

Fourteen adult, mongrel cats of either sex and 15 adult, New Zealand white rabbits of either sex were used. Surgical procedures in both species were similar and were performed under ether anaesthesia. The trachea was intubated for artificial respiration and a vein was cannulated for administration of drugs. The calvarium was widely exposed and 1/4 inch stainless steel, sheet metal screws were placed in the bone of cats over the sigmoid, suprasylvian and posterior lateral gyri bilaterally. The recordings were all unipolar and a common electrode was placed

in the bone over a frontal sinus. Similar screws were also used as electrodes in rabbits and were placed in relatively similar areas. After-discharges, developed in the frontal cortex were studied in both species. The sigmoid gyrus was stimulated with 5 ms square waves at 100 Hz for 5 s with amplitudes that varied from 1 to 4·5 V depending on the threshold of the cortex. Recordings were made immediately after the stimuli were turned off. Incisions and pressure points of the animals were infiltrated with 2% procaine before the ether was withdrawn, and repeated when necessary. The animals were paralysed with gallamine triethiodide or tubocurarine hydrochloride and maintained on artificial respiration. Body temperature was maintained with thermistor-controlled heat lamps. Electrical potentials were recorded on an Offner type T electroencephalograph at least 1 h after the ether had been withdrawn. Both drugs were dissolved in distilled water and administered intravenously in doses calculated for free base.

RESULTS

Three rabbits were used to examine the effects of fenfluramine on cortical potentials. Doses of 8 mg/kg did not alter the electrical activity markedly. All three animals were alert during the control period as only low voltage fast activity was seen in the e.e.g. The administration of fenfluramine resulted in only a slight reduction in the amplitude of these waves.

To slow the cortical potentials, pentobarbitone (10 mg/kg) was given intravenously to three rabbits. Fenfluramine (8 mg/kg) given to these animals reduced the amplitude and increased the frequency of the cortical waves (Fig. 1). The electrical potentials were markedly desynchronized in all three animals.

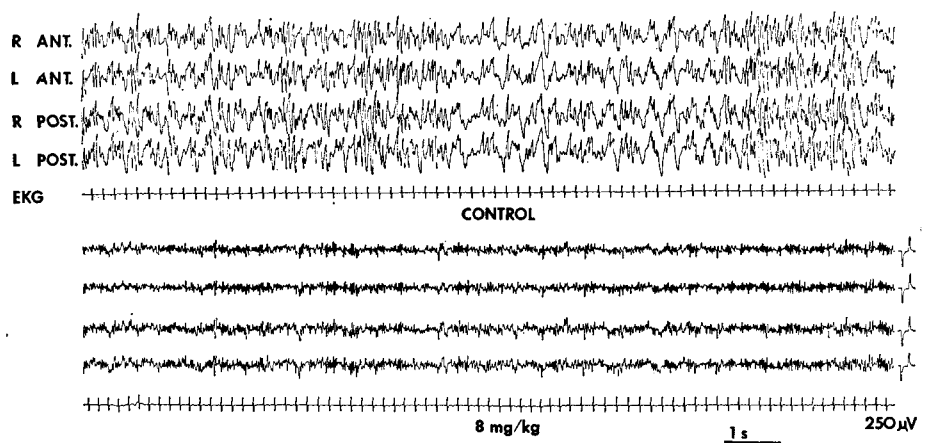

FIG. 1. Desynchronisation of pentobarbitone-slowed waves by fenfluramine in a rabbit. The cortical waves in the upper tracing have been slowed by the i.v. administration of pentobarbitone (10 mg/kg). Ten min later desynchronization of the slow waves was produced by fenfluramine (8 mg/kg) given i.v. ANT. = anterior cortex; POST. = posterior cortex. All recordings were monopolar with the common electrode in the frontal bone.

As shown by Foxwell & others (1969), cats respond to fenfluramine with slowing of the cortical waves and behavioral sleep. The findings with three cats given fenfluramine (8 mg/kg) confirmed the previous studies and, in contrast to the findings in rabbits, slow waves in the e.e.g. tracings were produced. Two other cats were given pentobarbitone (20 mg/kg) followed in 10 min by fenfluramine (10 mg/kg).

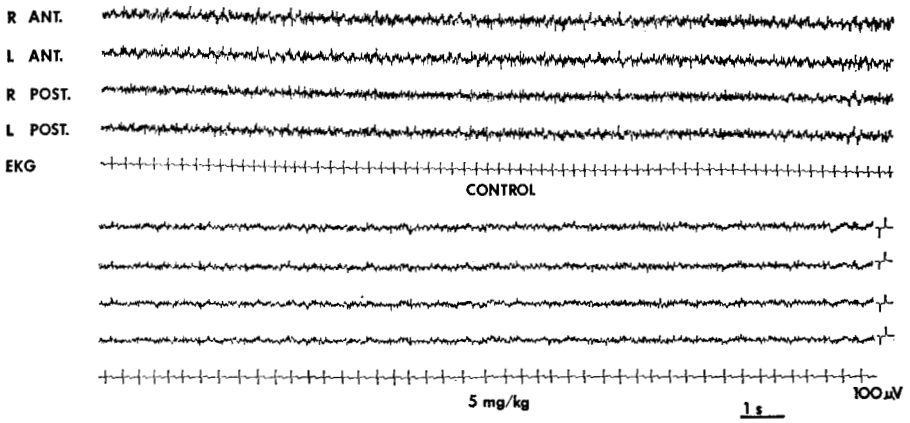

FIG. 2. Effect of norfenfluramine on cortical potentials in a rabbit. Like fenfluramine, norfenfluramine (5 mg/kg) given i.v. lowered the amplitude of the waves within 5 min without producing much change in frequency. Notations as in Fig. 1.

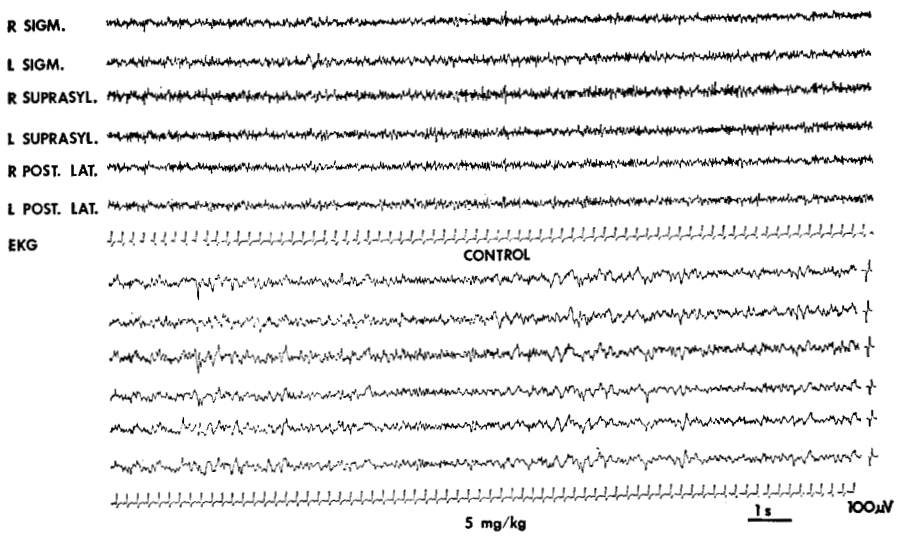

FIG. 3. Slowing of cortical potentials in a cat by norfenfluramine. The low voltage, fast activity in the control tracing was markedly slowed by the adminstration of norfenfluramine (5 mg/kg) (lower tracing). This effect was seen almost immediately and lasted for 4 h. SIGM. = sigmoid gyrus; SUPRASYL = suprasylvian gyrus; POST.LAT. = posterior lateral gyrus.

The pentobarbitone produced spindling which was not modified by the fenfluramine.

The effects of norfenfluramine (5 mg/kg) on cortical potentials were studied in three rabbits. Fig. 2 exemplifies a typical experiment. Low voltage fast activity dominated the control tracing and, after norfenfluramine, cortical activity was reduced in amplitude without apparent change in frequency of the waves although background slow waves were more prominent. In similar experiments at the same dose in three cats cortical activity was markedly slowed (Fig. 3).

The metabolite was also studied in rabbits and cats that had been given pentobarbitone (10 mg/kg). Spindling in the e.e.g. of two such rabbits was abolished and replaced by fast activity after norfenfluramine (5 mg/kg). In two cats, however, the spindling was unchanged by the same dose of the metabolite.

The effects of norfenfluramine on cortical after-discharges were studied in two rabbits. Fig. 4 shows that 5 mg/kg completely abolished this type of evoked potential without producing slow waves in the tracing. Both animals responded in the same way. Identical results were obtained in two other rabbits using fenfluramine (8 mg/kg). Norfenfluramine (5 mg/kg) in two cats produced similar responses to the rabbits in that the cortical after-discharge was completely abolished but in the cats, cortical slowing was also produced (Fig. 5). The cortical after-discharge was abolished in two other cats after the administration of fenfluramine (8 mg/kg), confirming the results of Foxwell & others (1969).

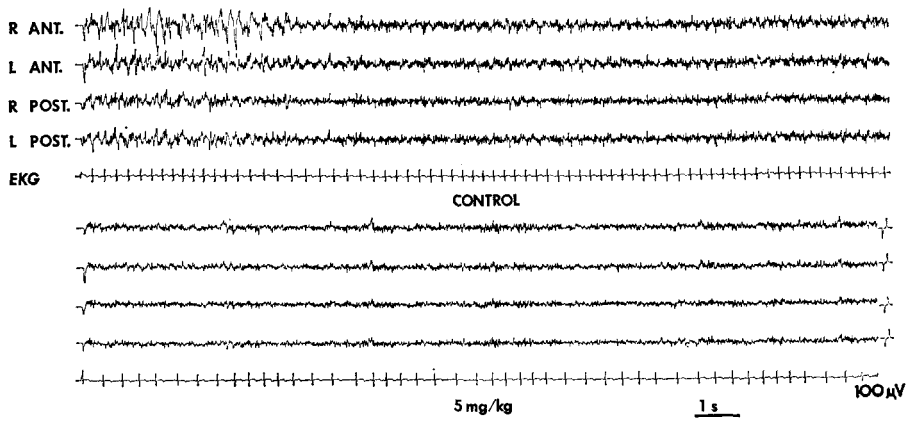

FIG. 4. Blockade of cortical after-discharges in a rabbit by norfenfluramine. After-discharges were produced in the upper tracing by stimulating the right frontal cortex with 2 V at a frequency of 100 Hz immediately before recording was made. Ten min after norfenfluramine (5 mg/kg) was given similar stimuation did not produce after-discharges (lower tracing). Similar results were obtained with fenfluramine. Notations as in Fig. 1.

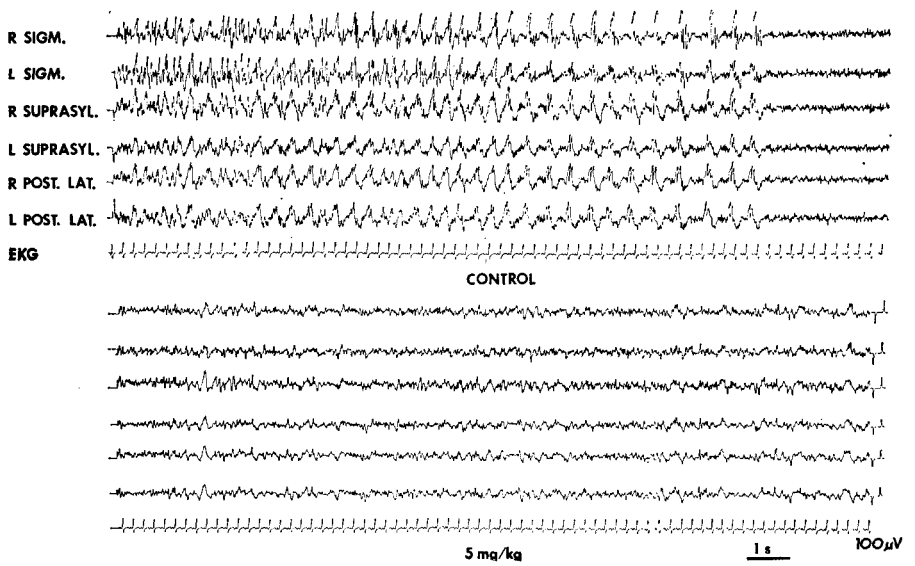

FIG. 5. Cortical after-discharges in a cat were abolished by norfenfluramine. Cortical after-discharges, produced as indicated in Fig. 4, were replaced by slow waves after the administration of norfenfluramine (5 mg/kg) (lower tracing). Similar results were obtained with fenfluramine. Notations as in Fig. 3.

DISCUSSION

The results show a species difference in the responses of rabbits and cats to fenfluramine and norfenfluramine. In general, rabbits were stimulated by both drugs and cats were depressed or sedated. The finding of a central nervous system stimulant action of fenfluramine in rabbits is in agreement with the report by Mayer & others (1970). Schmitt & Le Douarec (1965) on the other hand, found that fenfluramine produced a mixture of stimulant and sedative effects in rabbits. The only depressant action that we found in rabbits was the blockade of cortical after-discharge by both fenfluramine and norfenfluramine, but extensive subcortical studies were not done. A similar dual action of fenfluramine in cats was reported by Foxwell & others (1969) who showed that fenfluramine stimulated some subcortical structures while it depressed the cortex. The present findings show that the action of norfenflura mine on the cortex of the cat and rabbit is essentially the same as that of fenfluramine.

We have suggested previously (Funderburk & Ward, 1970) that the central nervous system stimulant action of fenfluramine in rabbits may be due to an active metabolite, norfenfluramine. Bruce & Maynard (personal communication) found that fenfluramine is metabolized to norfenfluramine in calves and rabbits and to a lesser extent in man; and Chandler, Dannenburg & others (1970) have shown that fenfluramine also has a central nervous stimulant action in calves. It was tempting to believe that cats metabolize the drug in a different manner, producing no norfenfluramine and consequently no stimulation. Bruce & Maynard (personal communication) found, however, that the cat and rabbit metabolize fenfluramine to norfenfluramine in about the same amounts and in the same time. We now have shown that norfenfluramine, like the parent compound, fenfluramine, has a predominantly stimulating action in rabbits but a predominantly sedative action in cats. The mechanism for the species difference may possibly be related to the unpublished observation of DaVanzo & Ruckart who have shown that fenfluramine significantly lowers the concentration of brain 5-hydroxytryptamine in cats but only slightly lowers the concentration of this amine in rabbits.

REFERENCES

Bruce, R. B. & Maynard, W. R. (1968). *J. pharm. Sci.*, **57**, 1173–1176.

Campbell, D. B. & Moore, B. W. R. (1969). *Lancet*, **2**, 1307.

Chandler, P. T., Dannenburg, W. N., Polan, C. E. & Thompson, N. R. (1970). *J. Dairy Sci.*, **53**, 1747–1756.

Colmore, J. P. & Moore, J. D. (1966). *J. New Drugs*, **6**, 123.

Duncan, E. H., Hyde, C. A., Regan, N. A. & Sweetman, B. (1965). *Br. J. clin. Pract.*, **19**, 451–452.

Fink, M. & Shapiro, D. M. (1969). *Electroenceph. clin. neurophysiol.*, **27**, 710.

Foxwell, M. H., Funderburk, W. H. & Ward, J. W. (1969). *J. Pharmac. exp. Ther.*, **165**, 60–70.

Funderburk, W. H. & Ward, J. W. (1970). *J. Pharm. Pharmac.*, **22**, 786–787.

Hill, R. C. & Turner, P. (1967). *Ibid.*, **19**, 337–338.

Jesperson, S., Bonaccorsi, A. & Garattini, S. (1969). *Ibid.*, **21**, 558–559.

Le Douarec, J. C., Schmitt, H. & Laubie, M. (1966). *Archs int. Pharmacodyn. Thér.*, **161**, 206–232.

Mayer, S. R., Southgate, P. J. & Wilson, A. B. (1970). *J. Pharm. Pharmac.*, **22**, 239–240.

Riley, I., Corson, J. Haider, I. & Oswald, I. (1969). *Lancet*, **2**, 1162–1163.

Schmitt, H. & Le Douarec, J. C. (1965). *Thérapie*, **20**, 111–120.

Traherne, J. B. (1965). *Practitioner*, **195**, 677–680.

Ziance, R. & Kinnard, W. J. (1967). *Pharmacologist*, **9**, 244.