Laboratory of Subcellular Ecology,
Institute of Plant and Animal Ecology,
Ural's Branch of U.S.S.R. Academy of Sciences,
8 *Marta Street*, 202, *Sverdlovsk, U.S.S.R.*

YU. P. VEDERNIKOV

October 31, 1969

REFERENCES

MAYNERT, E. (1967). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **26**, 1111–1114.
SANGAILO, A. K. (1962). *Proc. Sverdlovsk Med. Inst.*, **35**, 5.
VEDERNIKOV, YU. P. & AFRIKANOV, I. I. (1969). *J. Pharm. Pharmac.*, **21**, 845–847.

Central nervous system stimulant action of fenfluramine in rabbits

Fenfluramine is an anorexic drug which, although structurally related to amphetamine, has been described as having no central stimulant activity in animals or man (Le Douarec & Schmitt, 1964; Hill & Turner, 1967; Santer, 1968). Recently, Jespersen, Bonaccorsi & Garattini (1969) have shown that, like amphetamine, fenfluramine causes hyperthermia and clear signs of central nervous system excitation in mice treated with a combination of dopa and the monoamine oxidase inhibitor, pheniprazine. Although these experimental conditions are not comparable with those of the normal therapeutic use of fenfluramine, the findings are consistent with recent clinical reports of overdosage indicating that the drug can cause stimulation of the central nervous system in man (Riley, Corson & others, 1969; Gold, Gordon & others, 1969; Fleischer & Campbell, 1969; Campbell & Moore, 1969). Moreover, work in this laboratory has provided direct evidence of a cortical stimulant action of fenfluramine in rabbits.

Male adult rabbits, 3·5–5 kg, were prepared with indwelling stainless steel electrodes, placed superficially on the dura over the motor and occipital areas of the cerebral cortex. After complete recovery from the operation, the animals were trained to sit quietly in stocks for recording of electrocorticograms (ECoG). The normal ECoG showed an alert pattern, but after the intravenous administration of equi-anorectic doses of dexamphetamine sulphate (2 mg/kg) or fenfluramine hydrochloride (8 mg/kg) further arousal occurred although the effect was slight and barely distinguishable from the response to intravenous saline. In other experiments, to facilitate more quantitative evaluation of this effect, an ECoG pattern resembling deep sleep was first produced by the administration of pentobarbitone: under these circumstances, both anorectic drugs showed a clear-cut alerting action.

A comparison of the effects of dexamphetamine sulphate (2 mg/kg), fenfluramine hydrochloride (8 mg/kg) and normal saline (1 ml/kg) injected intravenously 30 min after an intravenous dose of pentobarbitone (20 mg/kg) was made in six rabbits using a cross-over design with an interval of at least two days between drug treatments. Recordings of ECoG were taken for 90 min after the administration of dexamphetamine or fenfluramine and their effects during this time were scored on a scale of 0 to 6, ranging from maximal arousal with persistent body movement artefact (score 0), to stage 4 sleep with low frequency, high amplitude records (score 6). Fig. 1 shows the abrupt change from an alert ECoG pattern to deep sleep after the administration of pentobarbitone; in contrast to the subsequent gradual lightening of sleep after intravenous saline administration, both dexamphetamine and fenfluramine caused a rapid and complete ECoG arousal accompanied by body movement artefacts, widely dilated pupils and intermittent masticatory movements.

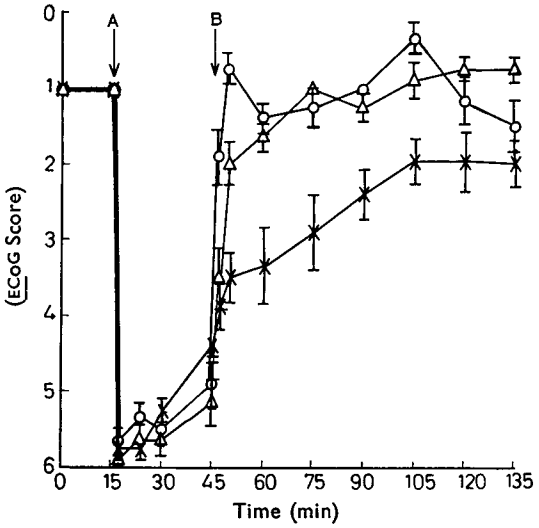

FIG. 1. Alerting effect of fenfluramine and dexamphetamine on the electrocorticogram in rabbits. At A, 20 mg/kg of pentobarbitone injected intravenously; at B, intravenous injections of 1 ml/kg of saline (x – x), 2 mg/kg of dexamphetamine sulphate (△ – △) or 8 mg/kg of fenfluramine hydrochloride (○ – ○). Each point represents the mean of four observations (± standard error).

This alerting action of fenfluramine on the ECoG in rabbits provides further evidence of its amphetamine-like stimulant properties in animals, an observation which is consistent with EEG results obtained in man early during recovery from overdosage.

Department of Pharmacology,
John Wyeth & Brother Ltd.,
Huntercombe Lane South,
Taplow, Maidenhead, Berks, U.K.

SUSAN R. MAYER
P. J. SOUTHGATE
A. B. WILSON

January 1, 1970

REFERENCES

CAMPBELL, D. B. & MOORE, B. W. R. (1969). *Lancet*, **2**, 1307.
FLEISCHER, M. R. & CAMPBELL, D. B. (1969). *Ibid.*, **2**, 1306–1307.
GOLD, R. G., GORDON, H. E., DA COSTA, R. W. D., PORTEOUS, I. B. & KIMBER, K. J. (1969). *Ibid.*, **2**, 1306.
HILL, R. C. & TURNER, P. (1967). *J. Pharm. Pharmac.*, **19**, 337–338.
JESPERSEN, S., BONACCORSI, A. & GARATTINI, S. (1969). *Ibid.*, **21**, 558–559.
LE DOUAREC, J. C. & SCHMITT, H. (1964). *Thérapie*, **19**, 831–841.
RILEY, I., CORSON, J., HAIDER, I. & OSWALD, I. (1969). *Lancet*, **2**, 1162–1163.
SANTER, N. (1968). *Br. med. J.*, **2**, 559.