Zusammenfassung. Während einstündiger epiduraler Applikation von 25% KCl zeigte sich bei Ratten eine Abnahme der elektrischen Aktivität im homolateralen Cortex und Striatum (spreading depression), die nach Entfernung des KCl reversibel war. Mit dem Auftreten von EEG-Veränderungen erfolgte im Gehirn auch ein reversibler Anstieg der Homovanillinsäure, nicht aber des Dopamins (DA), wahrscheinlich als Ausdruck eines gesteigerten DA-Umsatzes. Es wird geschlossen, dass während unilateraler epiduraler KCl-Applikation eine Inaktivierung des homolateralen Striatums besteht, welche möglicherweise durch Desaktivation einer inhibitorischen cortico- und/oder striato-nigralen Bahn zu einer Erhöhung des DA-Umsatzes führt,

L. PIERI, G. BARTHOLINI,
H. H. KELLER and A. PLETSCHER

Research Department, F. Hoffmann-La Roche & Co. Ltd, CH-4002 Basel (Switzerland), 2 November 1972.

Effect of Long-Term Fenfluramine Treatment on Drug-Metabolism in Rat

Fenfluramine, N-ethyl-α-methyl-3-(trifluoromethyl)-phenethylamine, is structurally related to amphetamine, has anorexic activity, but has been claimed to be devoid of the central nervous system stimulating activity[1]. Its acute and chronic toxicity have been evaluated in various species[2]. Fenfluramine is metabolized by dealkylation and probably by sidechain oxidation. The main metabolite of fenfluramine in human urine is m-trifluoro-methyl-hippuric acid[3]. We have been interested to know whether long-term fenfluramine treatment interfers, and to what extent, with the drug metabolizing enzymes of rat liver.

Materials and methods. Male Sprague-Dawley rats weighing 250–300 g were divided into 8 groups of 5 each. The animals received food and water ad libitum. Once a day they were given by stomach tube fenfluramine hydrochloride aqueous solution either 10 mg/kg (2 groups), 25 mg/kg (2 groups) or 50 mg/kg (2 groups). The 2 control groups received only water. One group of each dose level were decapitated 3 weeks and the others 8 weeks after the first dose. Livers were removed and homogenized in 4 volumes of 0.1*M* phosphate buffer of pH 7.4. The 105,000 × *g* microsomal fraction was used for the determinations of the activities of benzpyrene hydroxylase (BPH)[4], N-methyl-aniline demethylase (MAD)[5] and uridine diphosphoglucuronyl transferase (UDPGT)[6]. The cytochromes P-450 and b_5 were quantitated as described by OMURA and SATO[7]. Significance of difference from controls was calculated using the Student's *t*-test.

Results and discussion. In contrast to numerous amphetaminelike drugs, fenfluramine has been reported to produce greater loss of weight and fewer side-effects[8]. In our studies we found a slight reduction in food consumption and a retardation of weight gain which, however, was significant ($p < 0.05$) only in the group receiving the largest dose (50 mg/kg) of fenfluramine for 8 weeks. The animals receiving 25 or 50 mg/kg of fenfluramine daily p.o. showed hyperexcitability at the beginning of the treatment. This is contradictory to many other studies[9–11], which indicate rather a sedative effect, but is in agreement with those of EVERETT et al.[12] who observed that a mean dose of 6.1 mg/kg of fenfluramine given i.p. increased substantially the motor activity in rats. Interestingly enough, it has been shown by COSTA et al.[13] that fenfluramine possesses similar types of action on brain amines to amphetamine, e.g. it depletes the brain noradrenaline content.

In both our trials the doses of 25 and 50 mg/kg caused a significant increase in the relative liver weights shown in Table I, but in histological examinations no morphological changes could be found. The increase in the relative liver weight is common to many inducing agents because they produce proliferation of the endoplasmic reticulum and increase the protein content of the liver. As can be seen in Table II, both higher doses of fenfluramine really stimulated the drug metabolizing capacity of the rat liver microsomes. This effect is most clearly seen as an enhancement of MAD activity and the amount of Cytochrome P-450. The inducing effect was already maximal after 3 weeks' treatment. Fenfluramine causes a Type I differential spectrum when binding with Cytochrome P-450 (unpublished observation) which indicates that its metabolism may be accelerated by a phenobarbital-type of inducing agents. It has recently been shown that fenfluramine may also stimulate its own metabolism[14], which possibly explains the disappearance of the hyperexcitability mentioned and the lack of toxic symptoms after 8 weeks' treatment with the dose up to about half of the LD 50, which, according to GILBERT et al.[2], is 126 mg/kg.

Table I. Relative liver weights of rats receiving 10, 25 and 50 mg/kg of fenfluramine hydrochloride for 3 and 8 weeks

Fenfluramine (mg/kg)	3 weeks treatment	8 weeks treatment
Controls	2.69 ± 0.09	2.56 ± 0.19
10	2.91 ± 0.33	2.80 ± 0.23
25	3.24 ± 0.39[a]	3.33 ± 0.26[a]
50	3.61 ± 0.33[b]	3.47 ± 0.08[b]

The values are expressed as g liver/100 g body weight ± SD. Significance of difference from controls shown by [a] $< p$ 0.01; [b] $< p$ 0.001.

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Table II. Effect of 3 and 8 weeks fenfluramine administration on the drug metabolizing activity of rat liver

Fenfluramine (mg/kg)	BPH relat. fl. u./h/g × 10^4) 3 weeks	8 weeks	MAD (μg aniline/h/g) 3 weeks	8 weeks	UDPGT (μmol glucuronide/h/g) 3 weeks	8 weeks
Control	1.34 ± 0.29	1.56 ± 0.81	95.6 ± 22.1	107.2 ± 12.3	12.7 ± 2.6	9.1 ± 2.8
10	1.59 ± 0.32	1.49 ± 0.57	115.4 ± 14.7	105.3 ± 16.5	15.4 ± 5.2	15.7 ± 5.6
25	1.57 ± 0.14	2.37 ± 0.88	152.2 ± 29.4[b]	142.2 ± 21.4[a]	18.0 ± 2.6[b]	18.9 ± 2.2[c]
50	1.74 ± 0.64	2.26 ± 1.24	177.9 ± 22.1[c]	174.6 ± 15.3[c]	24.2 ± 6.5[b]	21.1 ± 5.4[b]

Fenfluramine (mg/kg)	Cyt b_5 424–410 nm/g 3 week	8 weeks	Cyt P-450 450–500 nm/g 3 weeks	8 weeks
Control	1.74 ± 0.42	1.35 ± 0.25	0.49 ± 0.12	0.45 ± 0.23
10	1.98 ± 0.31	1.49 ± 0.23	0.70 ± 0.30	0.52 ± 0.25
25	2.34 ± 0.27[a]	1.98 ± 0.25[b]	1.08 ± 0.43[a]	0.91 ± 0.29[a]
50	2.83 ± 0.14[b]	2.27 ± 0.36[b]	1.76 ± 0.48[b]	1.44 ± 0.37[b]

The activity figures are means ± SD. Significance of difference from controls shown by [a] $p < 0.05$; [b] $p < 0.01$ and [c] $p < 0.001$.

So far there have been no publications concerning the possible stimulation of drug metabolism caused by fenfluramine in man. Our results, which clearly show that 3 weeks' fenfluramine treatment already significantly increases the hepatic drug metabolism in rat, indicate that the same may take place during the chronic fenfluramine treatment in humans. This must be taken in account if fenfluramine treatment is started in patients who are, for instance, maintained on an anticoagulant therapy.

Zusammenfassung. Nachweis, dass Fenfluramin in Dosen von 25 und 50 mg/kg p.o. Arzneimittel abbauende Enzyme stimuliert und die Cytochromen b_5 und P-450 in der Rattenleber vermehrt. Der induzierende Effekt ist bereits nach 3 Wochen maximal.

P. Arvela[15], N. T. Kärki[15], L. Nieminen[16], K. Bjondahl[16], and M. Möttönen[17]

Department of Pharmacology, University of Oulu, SF–90 100 Oulu 10 (Finland), Research Laboratories, Lääke and Medipolar Ltd., Turku; and Department of Forensic Medicine, University of Turku, Turku (Finland), 25 September 1972.

[15] Department of Pharmacology, University of Oulu, SF–90 100 Oulu 10, Finland.
[16] Research Laboratories, Lääke and Medipolar Ltd., Turku, Finland.
[17] Department of Forensic Medicine University of Turku, Turku, Finland.

Participation of Retinal Mechanisms in DMT Hallucinations

The induction of optical hallucinations by psychotomimetic substances led to great efforts to clarify the action of these drugs in the visual system. Investigations of electrically or light induced evoked potentials under the influence of D-lysergic acid diethylamide (LSD), which was known to produce behavioral blindness in experimental animals, yielded diverging results: intracarotid or intravenous application of LSD in high dosage depressed[1–4], LSD in low dosage enhanced[5,6] or did not change[7,8] the evoked responses. The depressing or blocking action of LSD on evoked responses was localized into the lateral geniculate body[1,3,9,10]. However, the necessity of intact optic nerves for the appearance of typical LSD hallucinations and the effect on the electroretinogram[11] suggest that retinal mechanisms participate in the effect of this drug, and this assumption was supported by the alteration of the optic tract's tonic discharge caused by LSD[12,8].

Methods. The effect of N,N-Dimethyltryptamin (DMT)[13], whose action is similar to LSD[4,10,14,15] but of shorter duration, on activity of retinal neurons was studied in 11 adult cats (2.5–4.0 kg), with special consideration given to spontaneous discharge highly affected in other brain structures[16,17]. During pentobarbital anesthesia (0,03 g/kg) the optic nerve was prepared. After the operation the cats were immobilized with gallamonium iodide. Action potentials from single optic nerve fibres were recorded using glass-insulated Pt-Ir microelectrodes and conventional amplification[18]. Spontaneous activity was analyzed with a computer of

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