

Table 11. 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 $\times 10^4$		MAD (μ g aniline/h/g)		UDPGT (μ mol glucuronide/h/g)	
	3 weeks	8 weeks	3 weeks	8 weeks	3 weeks	8 weeks
Control	1.34 $\pm$ 0.29	1.56 $\pm$ 0.81	95.6 $\pm$ 22.1	107.2 $\pm$ 12.3	12.7 $\pm$ 2.6	9.1 $\pm$ 2.8
10	1.59 $\pm$ 0.32	1.49 $\pm$ 0.57	115.4 $\pm$ 14.7	105.3 $\pm$ 16.5	15.4 $\pm$ 5.2	15.7 $\pm$ 5.6
25	1.57 $\pm$ 0.14	2.37 $\pm$ 0.88	152.2 $\pm$ 29.4 ^b	142.2 $\pm$ 21.4 ^a	18.0 $\pm$ 2.6 ^b	18.9 $\pm$ 2.2 ^c
50	1.74 $\pm$ 0.64	2.26 $\pm$ 1.24	177.9 $\pm$ 22.1 ^c	174.6 $\pm$ 15.3 ^c	24.2 $\pm$ 6.5 ^b	21.1 $\pm$ 5.4 ^b

Fenfluramine (mg/kg)	Cyt b ₅ 424–410 nm/g		Cyt P-450 450–500 nm/g	
	3 week	8 weeks	3 weeks	8 weeks
Control	1.74 $\pm$ 0.42	1.35 $\pm$ 0.25	0.49 $\pm$ 0.12	0.45 $\pm$ 0.23
10	1.98 $\pm$ 0.31	1.49 $\pm$ 0.23	0.70 $\pm$ 0.30	0.52 $\pm$ 0.25
25	2.34 $\pm$ 0.27 ^a	1.98 $\pm$ 0.25 ^b	1.08 $\pm$ 0.43 ^a	0.91 $\pm$ 0.29 ^a
50	2.83 $\pm$ 0.14 ^b	2.27 $\pm$ 0.36 ^b	1.76 $\pm$ 0.48 ^b	1.44 $\pm$ 0.37 ^b

The activity figures are means $\pm$ 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 b₅ und P-450 in der Rattenleber vermehrt. Der induzierende Effekt ist bereits nach 3 Wochen maximal.

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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 depressed¹⁻⁴, 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 electroretinogram¹¹ 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 amplification¹⁸. Spontaneous activity was analyzed with a computer of

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average transients (CAT 1000), the phasic response to diffuse light stimuli of 15 cd/m² intensity and 1 sec duration was recorded on film. For comparison, in 5 animals the light-induced cortical-evoked potentials were recorded from the optic projection area (midmarginal gyrus); 200 single responses to diffuse light stimuli of 15 cd/m² and 200 msec duration were averaged in the CAT 1000. The test substance DMT diluted in saline solution was injected into the internal jugular vein. Arterial blood pressure was monitored from the left carotid artery; only short lasting transient drug dependent changes were observed.

Results. The similarity of the DMT effect on the activity of retinal neurons with all the dosages tested (1–5 mg/kg), probably due to saturation with the lowest dosage, justified the pooling of the results for the presentation. In 8 neurons the spontaneous activity was recorded at least 10 min before and up to 50 min after the injection of the drug (Figure 1, curve 1): During the first few min the average spontaneous activity decreased, increased to levels below the resting rate until the 10th min, decreased again reaching a minimum after 20–40 min and thereafter recovered slowly (Fig. 1, curve 1). This long term depressing effect, seen in 7 of 8 neurons recorded before and after drug application, was studied also in a statistical way in experiments in which single neurons were not isolated long enough to investigate the time course of the drug effect. In these experiments, the activity of individual neurons was recorded at different times after the drug injection and compared to the discharge rate of 29 single units not influenced by DMT. The mean values of the activities of 11 neurons recorded 10 and 20 min, 9 units recorded 30, and 7 units recorded 40 and 50 min after DMT injection are shown in Figure 1, curve 2 and demonstrate also the depression and slow recovery of spontaneous activity after DMT. Due to tachyphylaxis a 2nd injection of DMT resulted in only a slight decrease of spontaneous discharge rate (8 neurons), a 3rd in an insignificant alteration (3 neurons).

The phasic response of the neurons to light stimuli was altered in B (on-center) – as well as in D (off-center) neurons (Figure 2) showing the same biphasic time course of the drug effect as the spontaneous discharge rate (Figure 1, curve 3). The response characteristic for the center stimulation ('on' in B- and 'off' in D-neurons) was depressed (Figure 2) but also the reaction of the field surrounding (reaction to 'off' in B- and to 'on' in D-neurons) was altered leading to inhibition of the neuron's afterdischarge following the specific response of the receptive field.

The amplitude of *visually evoked cortical potentials* was altered in dependence on the dosage of DMT. First surface positive and first surface negative wave of the primary complex¹⁹ were evaluated (Figure 1, curve 4). While low dosages (1–2 mg/kg) had a slight increasing effect in 2 experiments, higher dosages (2–8 mg/kg)

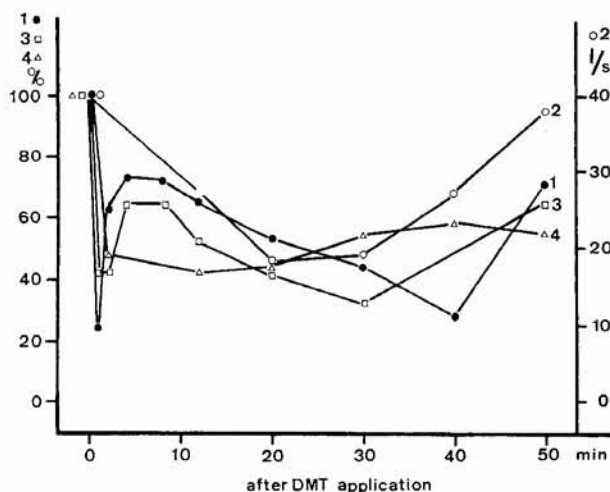


Fig. 1. Diagram of the time course of the DMT effect: curve 1 (●): percentual change of the average spontaneous activity in 8 neurons recorded before and after DMT application; curve 2 (○): average discharge rate of neurons recorded only at different time intervals after DMT in comparison to the activity in non-influenced neurons; curve 3 (□): percentual change of averaged primary light response in 8 neurons (3B and 5D); curve 4 (Δ): mean percentual change of amplitude between first positive and first negative wave of evoked responses in 5 animals.

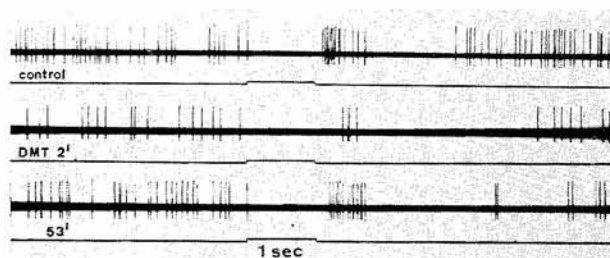


Fig. 2. Recordings from one D (off center) neuron before, 2 min and 53 min after DMT application (5 mg/kg) showing decrease (2 min) and recovery (53 min) of spontaneous activity and of light response. Light stimulus of 1 sec duration and 15 cd/m² is indicated on the lower trace of each recording.

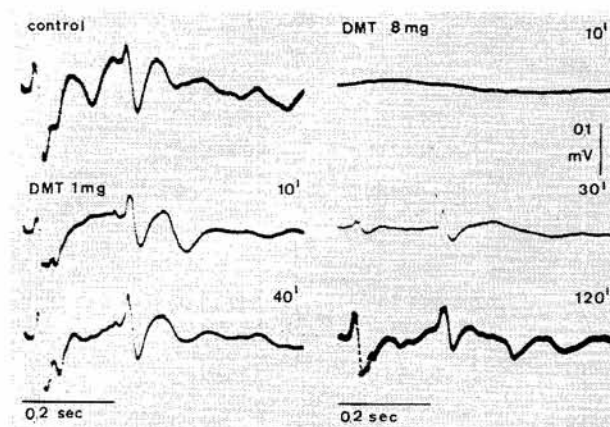


Fig. 3. Effect of 1 and 8 mg/kg DMT on visually evoked cortical potentials. Light stimulus: 0.2 sec. calibration: 0.1 mV, surface positive waves are drawn upwards.

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depressed or even abolished the evoked potentials in all experiments (Figure 3) with a maximum of 2–10 mV after injection (Figure 1, curve 4). The dosage-dependent alteration of the evoked responses corresponds to the diverging results obtained with LSD¹⁻⁸, with DMT only a depression was observed in optically⁴ and acoustically²⁰ evoked potentials. Extent of diminution of evoked potentials and time of recovery were dependent on given dosage, but again the first injection was more effective than the following applications. The increase of evoked responses observed in 2 experiments with low dosage of DMT may be due to the depressing effect on spontaneous background activity leading to an improved signal to noise ratio in the primary afferent channel. With higher dosage the transmission in the synapses of the sensory pathway is increasingly impaired and this results in a diminution or even abolition of the evoked potentials.

Discussion. It is evident from our results that DMT in dosages leading to hallucinations in man does not affect only the synaptic transmission in the lateral geniculate body but also the phasic response and the spontaneous activity of retinal ganglion cells. The depressing effect of DMT on the spontaneous activity is in correspondence with its action on other neurons^{14,17}, but does not fully agree with the LSD results of MOURIZ-GARCIA et al.⁸. The DMT-caused alteration of the spontaneous activity might be of some relevance for the origin of optic hallucinations: as described previously^{18,21,22}, maintained illumination decreases the discharge rate of retinal ganglion cells; the depression of the spontaneous activity caused by DMT might be interpreted by the brain as 'light' and this may contribute to the origin of abnormal reactions within brain structures which are also influenced, leading to hallucinations. Basing on the known interaction of LSD and DMT with 5-HT in other brain regions, especially raphe neurons^{14,15}, and on the activity depressing effect of intracarotid 5-HT on retinal gan-

glion cells²³, the DMT action on the activity of retinal neurons may be interpreted as indirect evidence for the existence of 5-HT as a transmitter in those retinal synapses, which are of special importance for the origin and/or transmission of spontaneous activity. That 5-HT was not yet found may be due to the high incidence of dopaminergic neurons in the retina²⁴, by whose fluorescence 5-HT terminals may be concealed²⁵.

Zusammenfassung. Intravenöse Injektionen von DMT (1–5 mg/kg) bewirkten neben einer Verkleinerung der visuell evozierten corticalen Potentiale und der licht-induzierten phasischen Reaktionen retinaler Neurone auch eine starke Verminderung der Spontanaktivität in Einzelfasern des N. opticus. Die Befunde sprechen für eine Beteiligung retinaler Mechanismen beim Zustandekommen optischer Halluzinationen und lassen 5-HT als retinalen Transmitter vermuten.

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