Disulfiram and the drug-induced effects on motility

SIR,—We have given disulfiram (50 or 100 mg/kg) intraperitoneally to white mice of R_3 strain, or to rats, once or three times at 2-hrly intervals and have found the level of noradrenaline in the brain to be decreased without affecting or increasing only slightly, the level of dopamine (Table 1). Determinations were made spectrophotofluorimetrically. One and a half hr after the last injection of disulfiram, cocaine hydrochloride was given subcutaneously 30 mg/kg to mice or 40 mg/kg to rats. After ½ hr the activity was registered by the photocell method during ½-hr sessions.

Disulfiram prevented the increase of activity induced by cocaine (Table 1).

A similar blocking effect was found by Maj & Przegaliński (1967) in mice with amphetamine-induced hyperactivity [5 mg/kg s.c., (±)-amphetamine sulphate].

Disulfiram was also given to reserpinized mice (1 mg/kg i.p.) in which sedation had been reversed by nialamide (100 mg/kg, i.p.) and DL-dopa (200 mg/kg, i.p.). Reserpine was injected 9 hr, disulfiram (50 mg/kg, i.p.) 6, 4 and 2 hr, nialamide 2 hr and dopa ½ hr before the test. Activity was assessed, as before, in groups of 10 mice.

Disulfiram prevented the stimulation induced by nialamide and dopa. The number of movements in reserpinized animals was 6 ± 5·1; in reserpinized animals treated with nialamide and dopa it was 158 ± 22·9, and in animals given disulfiram as well, it was 11 ± 4·2.

Analogous experiments were made with α-methyltyrosine methylester (50 mg/kg, three times at 3-hrly intervals, i.p.). Disulfiram was given as above, but the third injection being given with the third injection of α-methyltyrosine methylester. Pargyline (100 mg/kg, i.p.) was given 1½ hr, dopa (500 mg/kg, i.p.) ½ hr before the test. Activity was recorded in groups of 10 mice. The activity count in control mice was 183 ± 15·4 and in mice treated with α-methyltyrosine methylester it was 47 ± 11·3. After pargyline and dopa, stimulation was seen in mice given α-methyltyrosine methylester (196 ± 13·2), but not in mice pretreated with the ester-disulfiram combination (21 ± 12·8). All the results were significant ($P < 0.001$).

We have already reported that a similar preventive effect is obtained with disulfiram in mice given butyrophenones, and in these animals nialamide and dopa counteract sedation (Maj & Wielosz, 1967).

TABLE 1. THE EFFECT OF DISULFIRAM ON THE COCAINE-INDUCED HYPERACTIVITY IN MICE AND RATS

Animal	Disulfiram i.p. mg/kg	Activity counts	% of the control	P	Catecholamines % of normal values*	
					Dopamine	Noradrenaline
Mouse	—	386 (±32·3)	100·0	—	100·0	100·0
,,	1 × 50	355 (±71·1)	91·9	>0·6	92·7	61·9**
,,	1 × 100	272 (±62·4)	70·4	>0·1	101·0	54·7**
,,	—	340 (±41·5)	100·0	—	100·0	100·0
,,	3 × 50	212 (±31·4)	62·3	<0·05	126·8**	42·8**
,,	3 × 100	94 (± 9·7)	27·6	<0·001	126·8**	38·1**
Rat	—	193 (±23·5)	100·0	—	100·0	100·0
,,	1 × 50	198 (±49·2)	102·5	>0·9	96·5	82·8**
,,	3 × 50	49 (±14·8)	25·3	<0·001	114·0**	51·4**

Disulfiram was injected 2 hr or 6, 4 and 2 hr. and cocaine hydrochloride (30 mg/kg s.c. in mice and 40 mg/kg s.c. in rats) 30 min before the experiment. The activity was recorded in single mice during 30 min sessions. Figures represent the means of 10 animals.

* Content of catecholamines in brain expressed as a % of normal values from animals receiving disulfiram only (means of 3–7 experiments).

** $P < 0.05$.

The experiments reported seem to indicate that noradrenaline is essential for the changes in activity seen in these experiments. A contrary view exists ascribing significance to dopamine (Everett & Wiegand, 1962; Rossum & Hurkmans, 1964).

It is pertinent to consider whether it can be assumed that the described action of disulfiram is due to its influence on the level of the brain catecholamines and not to a direct influence on the receptors. Disulfiram is known not to affect the amphetamine stereotyped behaviour in rats (Maj & Przegaliński, 1967), which is ascribed to the release of dopamine in the extrapyramidal system (Ernst, 1967; Scheel-Krüger & Randrup, 1967). We were able to show that it does not block the stereotyped behaviour after apomorphine (2·5 mg/kg, s.c.) which arises from its direct action on the dopamine receptor (Anden, Rubenson & others, 1967; Ernst, 1967). An additional observation which contradicts the hypothesis that the action arises from blockade of the receptor is that in mice, in which increased spontaneous motility is induced by nialamide and dopa (271 $\pm$ 33), disulfiram administered after nialamide only partly prevents the stimulation (131 $\pm$ 54), but stimulation is prevented (4 $\pm$ 1·9) if disulfiram is administered before nialamide. This observation seems to contradict the view about the role of dopamine in these conditions. Disulfiram, in doses inducing the above-mentioned changes in the level of the brain catecholamines, likewise potentiates the convulsive action of leptazol given in subthreshold doses in mice.

Of course, the possibility of a direct action of disulfiram on the receptor has not yet been excluded, nor can we exclude the possibility of still another mechanism on enzymes other than dopamine-β-hydroxylase.

Acknowledgements. We wish to thank warmly Dr. O. Hornykiewicz from the Department of Pharmacology of Vienna University for photofluorimetric estimations of catecholamines. We thank Dr. H. Corrodi of AB Hässle, Göteborg, for the gift of α-methyltyrosine methylester and Chas. Pfizer & Co. for nialamide.

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October 11, 1967

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