The effect of diethyldithiocarbamate on amphetamine-induced behaviour in rats

Sodium diethyldithiocarbamate is a potent inhibitor of the enzyme dopamine-β-hydroxylase of brain *in vivo* (Carlsson, Fuxe & Hökfelt, 1967; Lippmann & Lloyd, 1969). It causes a depression of the conditioned-avoidance responses (Krantz & Seiden, 1968), but an excitation of agressive traits when combined with pargyline (Scheel-Krüger & Randrup, 1968). We report the effect of diethyldithiocarbamate on two aspects of amphetamine-induced-hyperactivity in rats.

Female albino rats (Wistar), 180–210 g, of the Lysolaje strain, were tested.

Sodium diethyldithiocarbamate (DDC, Lachema, Brno), and commercial solutions of amphetamine sulphate (AMPH, Psychoton) and imipramine (Melipramin, Vereinigte Heil and Nährmittelwerke Budapest) were administered intraperitoneally diluted in water at doses of DDC 400 and 500 mg/kg, AMPH 4 and 5 mg/kg, and imipramine 3 mg/kg. Leptazol (pentetrazolium; PhBS III) was dissolved in saline solution (0·5%), and administered by intravenous infusion.

The horizontal component of exploratory activity of the rats (number of crossed squares) was automatically recorded (Žalud, Mysliveček & others, 1970) in a darkened room at 23 $\pm$ 0·5° for 3 min. One day before, and on the same day as the test the animals were placed for 1 h in the room but not in the experimental box). The first measure of the parameter was made 60 min after administration of DDC or 30 min after AMPH, and the second measure 120 min after DDC or 90 min after AMPH.

The stereotyped movements provoked by amphetamine were seen in rats given 5 mg/kg. These were defined (Lapin & Shchelkunov, 1963) as a characteristic immobile posture with stereotyped movements of the head and front limbs; the numbers of rats making these movements were recorded at regular intervals.

In untreated rats, the horizontal component value for exploratory activity (Fig. 1) was 30 crossed squares in the first, and about 15 in the second measurement. DDC, 500 mg/kg, decreased the activity; this effect is more conspicuous at the first measurement. AMPH, 4 mg/kg, increased the activity, the corresponding values being twice as high as in the controls ($P < 0{\cdot}01$) at the first measurement, whereas at the second, there appeared no significant differences in the values.

When combined, the drugs (DDC administered 30 min before AMPH) gave a lower exploratory activity than in the AMPH group, but still higher than in the control group ($P < 0{\cdot}05$).

Table 1. *Duration of stereotyped movements provoked by amphetamine in rats pretreated with diethyldithiocarbamate or imipramine.* The numbers of rats producing the sterotyped movements are given. Diethyldithiocarbamate (400 mg/kg) and imipramine (3 mg/kg) were administered i.p. 30 min before amphetamine (5 mg/kg).

	No. of rats per group	Time (min) 30	40	50	60	75	90	105	120	135	150	165	180	210	240
Amphetamine control	7	0	2	2	3	6	7	7	7	4	3	2	2	0	—
Diethyldithiocarbamate + amphetamine	7	3	3	7	7	7	7	7	7	7	7	5	5	4	—
P				<0·01	<0·05						<0·05			<0·05	
Amphetamine control	7	2	2	6	6	6	6	6	6	4	3	2	1	0	0
Imipramine + amphetamine	6	1	1	3	5	6	6	6	6	6	6	6	6	6	6
P				<0·05									<0·05	<0·01	<0·01

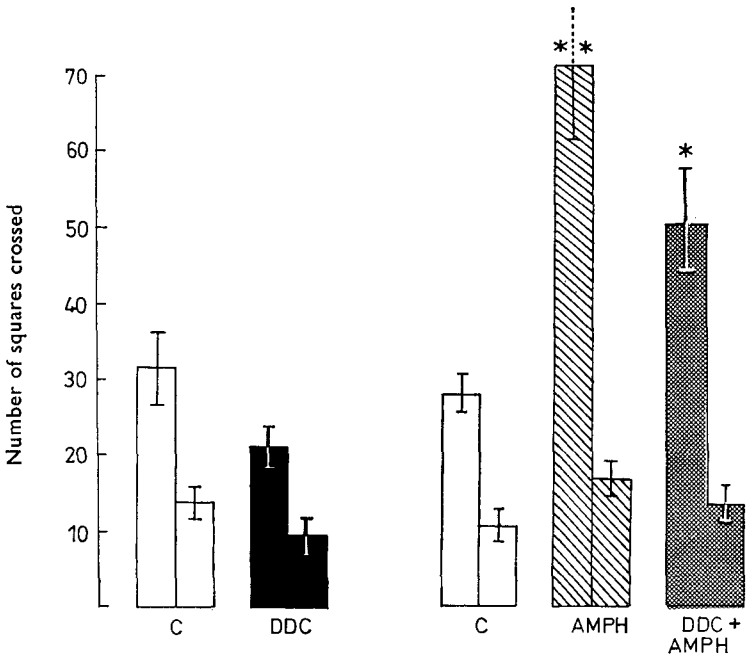

FIG. 1. Horizontal component of exploratory activity. Rats received i.p. distilled water (controls), diethyldithiocarbamate (DDC) 500 mg/kg, amphetamine (AMPH) 4 mg/kg and combination of DDC and AMPH respectively. Each pair of columns represent the first and second measurement. The mean value ± s.e. and the significance of differences (against the time corresponding control group) calculated by *t*-test are given, $^{**}P < 0.01$, $^{*}P < 0.05$.

Amphetamine stereotyped movements were perceptible (see Table 1) in most of the treated rats during 90 to 120 min after the AMPH, 5 mg/kg. DDC pretreatment, 30 min before AMPH, produced an earlier start, and a longer duration of these movements ($P < 0.01$); and they were seen in 4 rats in the DDC-pretreated group, but in none of the non-pretreated group at 210 min after AMPH.

Imipramine pretreatment, 30 min before AMPH, delayed the start of the movements ($P < 0.05$) but prolonged their duration beyond the limit of 240 min; all rats of the imipramine group, but none of the non-pretreated group, showed the movements 210 and 240 min after AMPH.

DDC possesses neither an antitremorine (Pfeifer, Galambos & György, 1966) nor an anticonvulsive action (since we have found that the amount of leptazol intravenously infused into mice to give convulsions remained unchanged after DDC, 500 mg/kg given 1 h before the infusion) but prolongs hexobarbitone sleep (Lange, Kästner & Jung, 1970; Pfeifer, Galambos & György, 1966). This is seen indirectly in that the administration of doses up to 500 mg/kg, as used in most experiments (ours; those of Pfeifer, Galambos & György, 1966; Krantz & Seiden, 1968; Scheel-Krüger & Randrup, 1968; Przegalinski & Kleinrok, 1970), is unlikely to provoke a non-specific cns depression of a toxic character. The hexobarbitone-potentiating effect is rather to be attributed to an inhibition of the liver microsomal oxidation by DDC (Lange & others, 1970).

The DDC effects on animal behaviour may be explained as an alteration of the dopamine-β-hydroxylase activity in the brain. The noradrenaline content is decreased after a single administration of DDC (Przegalinski & Kleinrok, 1970).

The dopamine content rises after repeated administration of DDC (Scheel-Krüger, & Randrup, 1968) or when given directly into the lateral ventricle of the brain (Kleinrok, Żebrowska & Wielosz, 1970). The changes are the result of dopamine-β-hydroxylase inhibition. Moreover, an increase of the tyrosine content in the brain probably caused by the feedback mechanism has been described (Magos & Jarvis, 1970). We found DDC to depress exploratory activity both in untreated and AMPH-stimulated rats on the one hand, while on the other it prolonged the duration of amphetamine stereotyped behaviour. Analogous results have been obtained by D'Encarnacao, D'Encarnacao & Tapp (1969) with AMPH-stimulated animals. These experiments support the hypothesis that large locomotory movements (AMPH-hypermotility) are provoked by release of noradrenaline, while the small movements, of stereotypic character, result from dopamine release (D'Encarnacao & others, 1969; Randrup & Scheel-Krüger, 1966). The DDC effects we found may be similarly explained in terms of the decrease of noradrenaline content (with a decrease of exploratory activity), and at same time, a dopamine rise (with a prolongation of amphetamine stereotyped behaviour).

DDC is considered to increase lethality in aggregated mice (Przegalinski & Kleinrok, 1970) and combined with pargyline provokes agressiveness in rats that is accompanied by a decrease in brain noradrenaline and a rise in dopamine (Scheel-Krüger & Randrup, 1968).

It seems that the elevated dopamine concentration in the brain should play a specific role in the phenomenon of adrenergic excitation described by Lapin & Shchelkunov (1963); hence it may be noted that the antidepressants like imipramine prolong the duration of amphetamine stereotypes and potentiate the toxicity of AMPH in aggregated mice (Simon, 1965).

The authors thank Dr Žalud and his colleagues of the Department of Pathophysiology, Charles University Medical Faculty, Plzeň, Czechoslovakia, for supplying the laboratory facilities.

Pharmacological Department,
Medical Faculty of Charles University,
Pilsen, Czechoslovakia.

O. MAYER
V. EYBL

May 25, 1971

REFERENCES

CARLSSON, A., FUXE, K. & HÖKFELT, T. (1967). *J. Pharm. Pharmac.*, **19**, 481–483.

D'ENCARNACAO, P. S., D'ENCARNACAO, P. & TAPP, J. T. (1969). *Archs int. Pharmacodyn. Thér.*, **182**, 186–189.

KLEINROK, Z., ŻEBROWSKA, I. & WIELOSZ, M. (1970). *Neuropharmacology*, **9**, 451–455.

KRANTZ, K. D. & SEIDEN, L. S. (1968). *J. Pharm. Pharmac.*, **20**, 166–167.

LANGE, P., KÄSTNER, D. & JUNG, F. (1970). *Acta biol. med. germ.*, **24**, K 29–33.

LAPIN, I. P. & SHCHELKUNOV, E. L. (1963). Proceedings of the Second International Pharmacological Meeting, Vol. 1, Pharmacology of Conditioning, Learning and Retention, p. 205. Pergamon Press, Czechoslovak Medical Press.

LIPPMANN, W. & LLOYD, K. (1969). *Biochem. Pharmac.*, **18**, 2507–2516.

MAGOS, L. & JARVIS, J. A. E. (1970). *J. Pharm. Pharmac.*, **22**, 936–938.

PFEIFER, A. K., GALAMBOS, E. & GYÖRGY, L. (1966). *Ibid.*, **18**, 254.

PRZEGALINSKI, E. & KLEINROK, Z. (1970). *Psychopharmacologia*, **16**, 409–418.

RANDRUP, A. & SCHEEL-KRÜGER, J. (1966). *J. Pharm. Pharmac.*, **18**, 752.

SCHEEL-KRÜGER, J. & RANDRUP, A. (1968). *Ibid.*, **20**, 948–949.

SIMON, P. (1965). *Thérapie*, **20**, 1123–1147.

ŽALUD, V., MYSLIVEČEK, J., SEMIGINOVSKÝ, B. & TILLER, M. (1970). *Activitas. nerv. sup.*, **12**, 157.