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The influence of certain psychotropic drugs on the biosynthesis of liver proteins *in vivo*

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THE FACT that the application of certain drugs induces[1–11] or, under proper conditions suppresses[1] the *in vivo* formation of microsomal enzymes suggests that such drugs may influence protein synthesis in general. In this investigation, amino acid incorporation into the liver proteins has been studied in mice treated with single doses of chlorpromazine, perathiepine, octoclothepine, methiadene, centrophenoxine, urethane and barbital.

EXPERIMENTAL

Male white mice, strain "H" (average weight 22 g) were used throughout. They were kept on a Larsen diet.

^{14}C-Algal protein hydrolysate has been obtained from The Radiochemical Centre, Amersham. The original solution has been buffered to pH 7·2 and diluted with physiological saline to attain the required activity. Perathiepine [10-(4-methylpiperazino)-10,11-dihydrodibenzo-(b,f)-thiepine,][13] octoclothepine [8-chlor-10-(4-methylpiperazino)-10,11-dihydrodibenzo-(b,f)-thiepine[14]] and methiadene [2-methyl-11(3-dimethylaminopropylidene)-6,11-dihydrodibenzo-(b,e)-thiepine[15]] have been prepared in this Institute. Centrophenoxine (dimethylaminoethylesther of 4-chlorphenoxyacetic acid) has been kindly supplied by the Bracco Industria Chimica S.p.A. Milano as Lucidryl®. Liquid scintillators were a produce of Tesla Works, Czechoslovakia. Other chemicals were purchased from commercial sources.

The drugs at doses indicated in the Table 1 were given either together with the amino acid mixture (2·5 μc per mouse) or after 24 hr of pretreatment. All substances were injected in a 0·1 ml solution intravenously into the tail vein. The animals were deprived of food after the application of the Algali protein hydrolysate and they were killed 24 hr later. The livers were quickly removed, blotted, weighed and homogenized with 3 ml of 0·4 N perchloric acid. Five millilitres of ethanol were added and the mixture was allowed to stand for 10 min at room temperature. The precipitate was spun down

TABLE 1. THE EFFECT OF INVESTIGATED COMPOUNDS ON THE INCORPORATION OF THE LABELLED AMINO ACID MIXTURE INTO MOUSE LIVER PROTEINS

Experiment	Control cpm/mg protein	Compound, dose	Pretreatment period (hr)			
			0		24	
			cpm/mg protein	Change (%)	cpm/mg protein	Change (%)
i	122 ± 15·5 (4)	Perathiepine, 10 mg/kg	*170 ± 31·8 (4)*	+39	*203 ± 34·5 (4)*	+67
ii	119 ± 23·5 (5)	Octoclothepine, 10 mg/kg	94 ± 36·0 (5)	−21	*151 ± 27·8 (5)*	+26
		Methiadene, 10 mg/kg	105 ± 32·2 (4)	−12	*196 ± 43·3 (5)*	+64
iii	107 ± 19·0 (5)	Chlorpromazine, 10 mg/kg	*142 ± 25·3 (5)*	+32	*161 ± 45·2 (4)*	+49
		Ocentrophenoxine, 250 mg/kg	113 ± 46·8 (5)	+5	119 ± 43·1 (4)	+10
iv	118 ± 12·7 (5)	Barbital, 50 mg/kg	93 ± 53·8 (5)	−21	*77 ± 18·1 (5)*	−33
		Urethan, 100 mg/kg	95 ± 25·1 (5)	−20	*95 ± 12·5 (5)*	−20

After the indicated pretreatment period, the animals were given 2·5 μCi of the Algal protein hydrolysate and they were sacrificed 24 hr later. The liver proteins were isolated as described in the Experimental part. Results are expressed as cpm/1 mg of protein, mean ± S.D. Numbers printed *in italics* denote statistically significant change ($P < 0·05$) from control.

and then washed with 8-ml quantities of 0·4 N perchloric acid–ethanol mixture (3:5), 0·4 N perchloric acid (three times), 1·6 N perchloric acid, 15 min at 70° (twice), ethanol 15 min at 50° (twice) and ethyl ether. The protein residue was dried on air, dissolved in 98% formic acid and the volume was made up to 5 ml. Of this solution, 0·5 ml was transferred into counting vials and mixed with 0·5 ml of dimethyl formamide, 2·0 ml of dioxane and 7·0 ml of a scintillating mixture containing 80% of SLT 31 and 20% of SGB 1 liquid scintillator. (SLT 31 contains 2-phenyl-5-(4-biphenyl)-oxadiazol 1,3,4 and 1,4 bis(2-phenyloxazolyl)-benzene in toluene. SGB 1 contains the same ingredients plus polyvinyltoluene gel.) The radioactivity was measured on the Tracerlab Model LSC 20. For the determination of proteins, 1·0 ml of the solution was placed onto pre-weighed planchets and dried to constant weight. The results were statistically examined with use of the Student's *t*-test.

RESULTS AND DISCUSSION

As it may be seen from the Table 1, all drugs studied except centrophenoxine alter the incorporation of amino acids into liver proteins. The lack of any effect of centrophenoxine may be attributed to the rapid elimination of this substance from the organism.[16] Urethane and barbital appeared to be moderate inhibitors. In the animals treated with perathiepine, chlorpromazine, octoclothepine and methiadene, the rate of protein synthesis was enhanced, especially after 24 hr of pretreatment.

Although six out of seven studied drugs influenced the incorporation of amino acids into mouse liver proteins, the total amount of liver proteins remained essentially unchanged. In addition, only octoclothepine caused a significant increase (by 23 per cent) of the liver size; other compounds were ineffective in this respect. These rather contradictory results may be due to the fact that the half-life of liver proteins[17] is much longer than the period, in which the rate of protein synthesis was changed. The part of liver proteins which is broken down and resynthetized during the action of drugs is relatively small and therefore the effect of drugs is not reflected by significant changes in total liver protein. In fact, liver size is usually increased after a prolonged application of these drugs.[18,19]

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