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Effects of mescaline and 2,5-dimethoxy-4-methylphenethylamine on sleeping time in mice

Mescaline shortens while 2,5-dimethoxy-4-methylphenethylamine (DMM-PEA) potentiates the sleeping time of pentobarbitone in mice (Ho, McIsaac & others, 1970; Ho, Tansey & others, 1970). We have now enquired whether the effect is explicable by an alteration in the metabolism of pentobarbitone.

Male Yale-Swiss mice, 25–30 g, were injected intraperitoneally with 50 μmol/kg of mescaline or DMM-PEA in saline. Control animals were given only saline. After 5 min a mixture of 40 mg/kg of sodium pentobarbitone and 100 μCi of [^{14}C]labelled pentobarbitone (New England Nuclear, U.S.A.) in saline was administered by the same route. The animals, groups of eight, were killed 30 and 60 min after pentobarbitone. The tissues from two mice of the same interval were combined and homogenized in three parts of water. Blood samples from a pool of two mice were centrifuged to separate the plasma. Tissue homogenates (0·1 ml) or plasma (25 μl) were treated with methanol and liquifluor, and assayed for ^{14}C by liquid scintillation. All values were corrected for 100% efficiency (channel ratio) and recovery. For chromatography, plasma or brain homogenate was extracted with diethyl ether (Cooper & Brodie, 1957). Sequential sections of paper (1 × 2·5 cm^2) from paper chromatograms were placed in counting vials, treated with methanol and liquifluor, and then assayed for ^{14}C. Sleeping time was recorded as the time between loss and return of the righting reflex after intraperitoneal injection of sodium barbitone (250 mg/kg) to mice.

At 60 min after intraperitoneal injection of [^{14}C]pentobarbitone, significant increases of specific activity were observed in the plasma and brain of animals pretreated with mescaline or DMM-PEA (Table 1). The two compounds also caused increases of radioactivity in liver at both 30 and 60 min intervals. The kidney concentration of pentobarbitone plus metabolites was higher than in the controls at 30 min, but decreased to the same level at 60 min.

From the chromatographic studies, the proportions of unchanged pentobarbitone and metabolites in plasma and brain of both experimental and control animals were calculated (Table 2). The recoveries of metabolites by ether extraction from the plasma and brain homogenates were 90 and 96% respectively. Decreases in the amounts of metabolites and increases in the unchanged pentobarbitone were observed in the 30 min plasma and 60 min brain samples of animals treated with DMM-PEA;

however, these changes in ratio of metabolites and the unchanged compound did not appear in the animals receiving mescaline.

The results in Table 3 show that DMM-PEA doubled the barbitone sleeping time in mice, but mescaline was without effect.

The increase in the pentobarbitone sleeping time in mice by DMM-PEA may arise from its ability to decrease the rate of metabolism of pentobarbitone in brain and plasma. But, the same argument cannot explain the effect of DMM-PEA in lengthening the barbitone sleeping time, because barbitone is largely unmetabolized in mice (Roth Leiper & others, 1949). The prolongation of pentobarbitone sleeping time in mice by oestrogen has been reported (Blackham & Spencer, 1969), and decreases in both the rate of metabolism and the renal clearance of pentobarbitone by this compound were offered in explanation of its action. DMM-PEA-induced reduction of renal excretion of barbiturates is likewise possible, in view of the increases of concentrations of pentobarbitone in brain, kidney, liver and plasma of the experimental animals.

Table 1. *Distribution of radioactivity in mouse tissues*

	nCi Specific activity (nCi/g tissue) ± s.e.					
	Control		DMM-PEA		Mescaline	
Tissue	30 min	60 min	30 min	60 min	30 min	60 min
Plasma†	89·64 ± 6·03	69·71 ± 3·60	92·91 ± 4·32	89·37 ± 1·73*	99·88 ± 6·48	97·66 ± 6·97*
Brain	71·32 ± 8·36	38·43 ± 2·93	72·92 ± 0·87	64·34 ± 7·57*	65·42 ± 2·79	60·93 ± 3·88*
Liver	192·50 ± 9·93	146·52 ± 5·56	224·98 ± 7·44*	201·36 ± 5·86*	236·33 ± 3·74*	198·38 ± 3·67
Kidney	140·41 ± 1·93	152·72 ± 11·57	160·98 ± 13·27*	145·64 ± 4·73	159·91 ± 8·47*	152·14 ± 6·66

* $P < 0{\cdot}01$
† Specific activity: nCi/ml

Table 2. *Percent unchanged pentobarbitone and metabolites in mouse plasma and brain*

Tissue	Metabolite No.†	Rf‡	Control 30 min	Control 60 min	DMM-PEA 30 min	DMM-PEA 60 min	Mescaline 30 min	Mescaline 60 min
	I	0·12	5·1 ± 0·5	3·2 ± 0·2	3·6 ± 0·2	4·4 ± 0·2	4·3 ± 0·3	4·8 ± 0·5
Plasma	II	0·58	48·1 ± 4·0	61·9 ± 2·1	36·9 ± 1·8*	52·3 ± 4·5	40·6 ± 2·2	58·7 ± 1·6
	III	0·90	46·8 ± 3·7	34·9 ± 2·4	59·5 ± 1·9*	43·2 ± 4·5	55·0 ± 2·6	36·5 ± 2·5
	I	0·12	1·1 ± 0·3	0·7 ± 0·2	0·3 ± 0·2	0·3 ± 0·1	0·2 ± 0·0	0·5 ± 0·1
Brain	II	0·58	4·6 ± 1·6	13·3 ± 1·2	3·3 ± 0·1	8·7 ± 1·2*	3·4 ± 0·6	12·6 ± 0·9
	III	0·90	94·3 ± 1·8	86·0 ± 1·2	96·4 ± 0·5	90·8 ± 1·0*	96·3 ± 0·5	86·9 ± 0·8

* $P < 0{\cdot}05$.
† I, pentobarbitone carboxylic acid; II, pentobarbitone alcohol; III, unchanged pentobarbitone (Cooper & Brodie, 1957).
‡ Paper chromatography in n-butanol saturated with 1% aqueous NH_4OH (Cooper & Brodie, 1957).

Table 3. *Effect of DMM-PEA and mescaline on barbitone and pentobarbitone sleeping time in mice.*

Treatment	Sleeping time (min) ± s.e. Barbitone	Sleeping time (min) ± s.e. Pentobarbitone
Control	237 ± 16 (6)	41·0 ± 1·1
DMM-PEA	427 ± 14* (6)	98·0 ± 8·5*‡
Mescaline	257 ± 16 (6)	34·4 ± 2·1†‡

Number in parentheses represent numbers of animals.
* $P < 0{\cdot}001$.
† $P < 0{\cdot}01$.
‡ Data from Ho, Tansey & others (1970).

Mescaline had no effect on the metabolism of pentobarbitone in mice. Although it also caused increases in accumulation of pentobarbitone in brain, plasma, liver and kidney, the pentobarbitone sleeping time in animals treated with mescaline was shortened. Furthermore, the barbitone sleeping time was unaffected. If the increase of concentration in the tissues of experimental animals was the result of an increase in binding of pentobarbitone by mescaline, a reduction of the "free" pentobarbitone for exerting hypnotic action could account for the resulting decrease of pentobarbitone sleeping time in mice.

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A comparison of the stereochemical requirements of cholinergic and anticholinergic drugs

None of the many theories which have been suggested to explain the observed behaviour of cholinergic and anticholinergic drugs at the muscarinic or postganglionic receptor account satisfactorily for all the experimental data (Goldstein, Aronow & Kalman, 1968). For example, it is difficult to explain why, although the dose-response curves for the antagonism of acetylcholine by atropine on the guinea-pig ileum are indicative of a competitive interaction (with both acetylcholine and atropine having at least one common point of attachment as a receptor site), the well known fact that the rate of washout of atropine from ileum is independent of the concentration of acetylcholine in the rinsing solution is not consistent with such a competitive interaction. There have been many attempts to explain this; for example, it has been suggested recently that the observed apparent competitive antagonism could result if the receptors were quite distinct, but that the presence of an antagonist at a site near to the cholinergic receptor could modify the cholinergic receptor in such a way that the affinity of the agonist for its receptor was reduced (Goldstein & others, 1968). In an attempt to assess whether or not cholinergic and anticholinergic drugs interact with a common receptor we have considered the structure-activity relations of a series of agonists and antagonists which are formally derived from acetylcholine.

Acetylcholine (I) may be converted into an anticholinergic drug by replacement of the acetyl group by a more bulky substituent such as 2-cyclohexyl-2-hydroxy-2-phenylacetyl (II) (Ellenbroek, Nivard & others, 1965). In such anticholinergic drugs the potency is critically dependent on the configuration of the benzylic carbon atom, the *R* enantiomer of II being 100 times as active as the *S* enantiomer (Table 1). Comparison of cholinergic esters of acetic acid and anticholinergic esters of *R*(−)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid may be made in the following manner.

1. Replacement of any of the *N*-methyl substituents in I by other alkyl groups reduces cholinergic activity whereas in II the nature of the *N*-substituents may vary over wide limits without appreciably reducing potency, and in some instances increase potency.