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THE EFFECTS OF DRUGS ON BARBITAL ANAESTHESIA IN MICE

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Abstract—The effects of drugs on barbital induction time in mice have been examined: special attention was paid to compounds known to potentiate hexobarbital anaesthesia in this species. Brain barbital concentrations at onset of anaesthesia were recorded after pre-treatment with reserpine, 5-hydroxytryptamine, chlorpromazine or benactyzine. All four drugs reduce the induction time of barbital anaesthesia without increasing its rate of brain penetration. Possible mechanisms of action are discussed. It is suggested that the criterion of reduced induction for barbital anaesthesia should not be regarded as necessarily indicating an increased permeability of the blood–brain barrier.

INTRODUCTION

BUTLER[1] has shown that the delay in onset of anaesthesia after an intravenous injection of barbital results from the hypnotic's slow rate of penetration into the brain. Prior administration of physostigmine halves this induction time by increasing the permeability of the blood–brain barrier to the barbiturate.[2] Other workers have since claimed that certain enzymes, notably trypsin, chymotrypsin and hyaluronidase,[3] or adrenalectomy,[4, 5] can shorten the induction time of barbital anaesthesia by altering the permeability of the blood–brain barrier. We therefore attempted to determine whether other drugs that potentiate barbiturates also affect the blood–brain barrier.

METHODS

Male fawn mice (GFF strain, body weight range 16—22 g) were used.

The induction time for barbital was measured by the method of Greig and Mayberry.[2]

Groups of ten mice were injected intravenously with sodium barbital (5·5 mg in 0·4 ml/20 g), each injection taking 20—30 sec. The interval between the injection and the loss of the righting reflex was taken as the induction time. The experiments were conducted at room temperature (approx. 19 °C), and groups of mice given barbital only were always included, to allow for day-to-day variations in response.

Brain barbital concentrations were determined by Butler's method.[1] Groups of four mice were injected intravenously with sodium barbital (5·5 mg in 0·4 ml/20 g) and then killed after intervals of 2, 5, 10, 15, 20, 25, 30 and 35 min. The brains from each group were weighed together and assayed for total barbital.

RESULTS

The changes in barbital induction time produced by pre-treating the mice with drugs known to increase the duration of hexobarbital hypnosis in mice are given in Table 1; the results in Table 2 refer to a miscellany of pharmacological agents.

TABLE 1. CHANGES IN INDUCTION TIME OF BARBITAL ANAESTHESIA PRODUCED BY DRUGS POTENTIATING HEXOBARBITAL HYPNOSIS

Drug	Dose (mg/kg)	Route	Time before barbital (min)	Group mean induction time (min. ± s.e.)*	
				Test	Control
5-Hydroxy-tryptamine	2·5	intraperitoneal	10	12·7±0·8	18·3±0·6
	5·0			10·0±0·6	
	20·0			7·7±0·4	
Reserpine	0·5	intraperitoneal	60	12·1±0·7	17·8±0·9
	2·0			8·0±0·4	
	5·0			5·2±0·4	
Chlorpromazine	0·5	intraperitoneal	5	11·3±0·8	18·1±1·0
	1·0			9·8±0·8	
	2·0			7·0±0·6	
Benactyzine	2·5	intraperitoneal	30	11·9±0·7	17·7±0·8
	10·0			10·5±0·7	
SKF525A	50	oral	40	17·3±0·9	17·6±0·9
	100			18·1±0·9	
Phenergan	2·5	intraperitoneal	15	14·1±0·8	18·4±0·9
	5·0			11·1±0·7	
Mepyramine	2·5	intraperitoneal	15	16·8±1·0	18·5±0·8
	5·0			13·2±0·8	
	10·0			10·5±0·3	

* Ten animals per group.

TABLE 2. CHANGES IN INDUCTION TIME OF BARBITAL ANAESTHESIA PRODUCED BY VARIOUS DRUGS INTRAPERITONEALLY

Drug	Dose (mg/kg)	Time before barbital (min)	Group mean induction time (min ± s.e.)*	
			Test	Control
Eserine	0·4	Immediate	21·5±0·6	18·4±0·6
	0·4	30	11·6±0·6	
Amphetamine	1·0	15	18·2±0·7	16·6±0·6
	2·5		20·2±0·9	
	5·0		27·2±1·0	
	10·0		31·4±1·1	
Metrazole	10·0	15	19·6±1·0	18·6±0·6
	20·0		18·2±0·7	
Nikethamide	10·0	15	17·0±0·8	17·7±0·6
	20·0		15·3±0·8	
Picrotoxin	1·0	15	17·8±0·9	18·6±0·9
Atropine	2·5	15	16·1±0·9	17·4±0·5
	5·0		15·0±0·9	
Lysergic acid diethylamide	1·0	5	18·0±0·5	19·8±0·6
	5·0	5	17·0±0·9	
	1·0	60	19·4±1·0	
	5·0	60	15·5±0·9	
Pilocarpine	1·0	15	15·5±0·4	16·9±0·6

* Ten animals per group.

Induction time was significantly reduced ($P < 0{\cdot}001$) by pre-treatment with reserpine, 5-hydroxytryptamine, chlorpromazine or benactyzine, but was unaffected by SKF.525-A (β-diethylaminoethyldiphenylpropylacetate). The decreases in induction time were not associated with increased rates of penetration into the brain by the barbital. In fact the brain barbital concentrations at the onset of hypnosis were significantly less than that found for control animals (Table 3). The results obtained

TABLE 3. BRAIN CONCENTRATION OF BARBITAL AFTER PRE-TREATMENT WITH DRUGS

Drug	Dose (mg/kg) intraperitoneal	Time before barbital (min)	Group mean induction time (min ± s.e.)*	Brain barbital concentration at induction (moles × 10^{-6}/g wet tissue)
Nil	—	—	17·9±0·7	1·12
5-Hydroxytryptamine	20·0	10	7·7±0·4	0·68
Reserpine	2·0	60	8·0±0·4	0·65
Chlorpromazine	2·0	5	7·0±0·6	0·79
Benactyzine	2·5	30	11·9±0·7	0·89

* Ten mice per group.

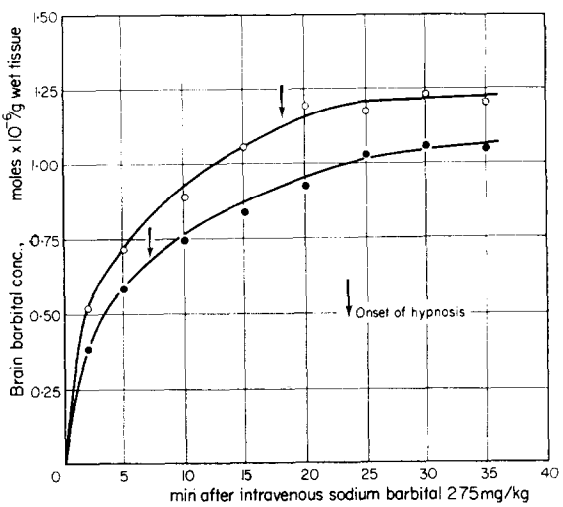

FIG. 1. The effect of reserpine on the rate of penetration of sodium barbital into mouse brain. ○——○ barbital alone; ●——● barbital 60 min after intraperitoneal reserpine 2·0 mg/kg.

with reserpine are illustrated in Fig. 1. The decrease in induction time produced by 5-hydroxytryptamine was partially reversed by pre-treatment with lysergic acid diethylamide 10 mg/kg i.p. (Table 4).

Certain analeptics—metrazole, nikethamide and picrotoxin—did not affect barbital induction time in small doses, but amphetamine (5 or 10 mg/kg) markedly increased it.

TABLE 4. MODIFICATION BY LYSERGIC ACID DIETHYLAMIDE OF THE REDUCTION IN BARBITAL INDUCTION TIME PRODUCED BY SEROTONIN

Group mean induction time — min ± s.e.*		
Control	10 min after after 5-hydroxytryptamine 20 mg/kg intraperitoneally	10 min after 5-hydroxytryptamine 20 mg/kg intraperitoneally and 1 hr after lysergic acid diethylamide 10 mg/kg intraperitoneally
17·8 ± 0·6	7·6 ± 0·6	13·2 ± 0·9

* Ten mice per group.

Of the other drugs tested, only the anti-histamines, phenergan and mepyramine reduced the induction time.

DISCUSSION

The results summarized above showed that pre-treatment of mice with reserpine, 5-hydroxytryptamine, benactyzine, chlorpromazine, phenergan or mepyramine reduced the delay in onset of barbital anaesthesia.

With reserpine, 5-hydroxytryptamine, benactyzine and chlorpromazine, the reductions were not the result of increased rate of penetration into the brain by the barbital, because the brain barbital concentrations at the onset of anaesthesia were less than normal. The reduced induction times might have resulted from increased sensitivity of the brain cells to barbital or have been reflections of the hypothermia produced by these drugs.[6–8]

The experiments recorded here showed that a decrease in the induction time of barbital anaesthesia did not necessarily imply an increased permeability of the blood–brain barrier.

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