THE INFLUENCE OF β-TETRAHYDRONAPHTHYLAMINE AND A DERIVATIVE ON THE CENTRAL EFFECTS OF 5-HYDROXYTRYPTAMINE, RESERPINE AND IPRONIAZID

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N-Methyl-*N*-propyl-β-tetrahydronaphthylamine, a specific antagonist of 5-hydroxytryptamine on the isolated rat uterus preparation, fails to inhibit 5-hydroxytryptamine potentiation of the hypnotic action of hexobarbitone in mice. The potentiating actions of reserpine and iproniazid are likewise unaffected. The action of β-tetrahydronaphthylamine as an antagonist of the potentiating action of 5-hydroxytryptamine on hexobarbitone sleeping time in mice has been confirmed, and it has also been shown to be an effective antagonist of the sleep prolonging effects of reserpine. β-Tetrahydronaphthylamine also shows a partial antagonism to iproniazid potentiation of hexobarbitone hypnosis. These results provide an example of the lack of parallelism between the central and smooth muscle actions of 5-hydroxytryptamine antagonists.

STUDIES of 5-hydroxytryptamine antagonists have indicated that there are drugs such as β-tetrahydronaphthylamine (β-tetra), which while altering the central actions of 5-hydroxytryptamine (5-HT), do not antagonise its actions on isolated smooth muscle preparations. 5-Hydroxytryptamine causes depression when injected into the lateral cerebral ventricle of cats[1], and causes prolongation of hexobarbitone hypnosis in mice[2]. β-Tetra antagonises both these effects[3]. On the other hand it has little action against 5-HT on the isolated rat uterus preparation[3,4]. These findings have been confirmed in this laboratory. β-Tetra has a slight anti-5-HT action on perfused rabbit ear vessels[3].

While investigating the pharmacological actions of a series of β-tetrahydronaphthylamine derivatives synthesised by Craig, Moore and Ritchie (unpublished) we have observed that *N*-methyl-*N*-propyl-β-tetrahydronaphthylamine (M-P. β-tetra) specifically inhibited the action of 5-HT on the rat uterus preparation in a concentration of $1:10^{-7}$. The present paper describes the effects of this derivative and of β-tetra on the duration of 5-HT potentiated hexobarbitone hypnosis in mice.

The effects of these two substances on the sleep-prolonging effects of reserpine have been investigated since Shore and others[5] have suggested that this action of reserpine is mediated through 5-HT. The effects of β-tetra and M-P. β-tetra on the potentiation of hexobarbitone hypnosis brought about by iproniazid, which produces an increase in endogenous brain 5-HT[6], have also been studied.

METHODS

Hexobarbitone (90–100 mg./kg.) was administered by intraperitoneal injection to albino mice of either sex weighing between 20 and 22 g. The

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doses used were 30 mg./kg. of 5-HT (as the creatinine sulphate), 1 mg./kg. of reserpine and 18 or 20 mg./kg. of iproniazid (Marsilid) as the phosphate. Both the 5-HT and the reserpine were given by intraperitoneal injection, while iproniazid was administered subcutaneously. An interval of one hour was allowed after the injection of 5-HT or iproniazid before the administration of hexobarbitone; with reserpine, however, a two hour

TABLE I

THE EFFECT OF β-TETRAHYDRONAPHTHYLAMINE HYDROCHLORIDE UPON THE SLEEPING TIME DUE TO HEXOBARBITONE, POTENTIATED BY 5-HYDROXYTRYPTAMINE CREATININE SULPHATE (5-HT), RESERPINE AND IPRONIAZID
(Room temperature 22°)

Drug	Dose in mg./kg.	Route	Mean sleeping time	Difference in sleeping times	t_s
Hexobarbitone ..	100	I.P.	26·4 ± 2·9 (22)		
				26·0 ± 1·5	17·6
Hexobarbitone + 5-HT	100 30	I.P. I.P.	52·5 ± 5·0 (11)		
				22·1 ± 1·2	14·0
Hexobarbitone + 5-HT + β-tetra	100 30 25	I.P. I.P. I.P.	26·0 ± 1·5 (12)		
Hexobarbitone ..	100	I.P.	22·3 ± 1·0 (10)		
				23·6 ± 3·6	6·5
Hexobarbitone + reserpine	100 30	I.P. I.P.	45·9 ± 4·9 (10)		
				20·1 ± 2·2	8·9
Hexobarbitone + reserpine + β-tetra	100 1 25	I.P. I.P. I.P.	25·6 ± 5·7 (8)		
Hexobarbitone ..	100	I.P.	23·1 ± 1·0 (24)		
				73·7 ± 8·6	8·6
Hexobarbitone + iproniazid	100 20	I.P. S.C.	96·8 ± 13·0 (12)		
				56·2 ± 11·0	5·1
Hexobarbitone + iproniazid + β-tetra	100 20 25	I.P. S.C. I.P.	40·6 ± 7·6 (11)		
Hexobarbitone ..	90	I.P.	12·8 ± 1·5 (11)		
				9·0 ± 0·9	10·0
Hexobarbitone + iproniazid	90 18	I.P. S.C.	22·0 ± 1·8 (11)		
				4·4 ± 0·7	5·8
Hexobarbitone + iproniazid + β-tetra	90 18 1	I.P. S.C. I.P.	17·6 ± 1·9 (11)		

The number in brackets after each mean sleeping time gives the number of animals in the group from which the tabulated mean value was calculated. The values appearing in the column headed "difference in sleeping times" refer to the differences between the mean sleeping times appearing in the preceding column immediately above the tabulated values, and those in the preceding column immediately below it. The *t*-test shows significant ($P < 0.001$) differences between the mean values compared.

interval was found preferable. The tests were performed in a thermostatically controlled cabinet adjustable from 5 to 40° ± 0·1°, usually set at 22°.

The sleeping time was measured as the time from the loss of the righting reflex to its reappearance within 30 seconds of placing the mouse on its back. Ten or more mice were used in each test group except in two experiments.

Each comparison between the hypnotic drug and potentiators or antagonists was made at the same time since the control sleeping time with hexobarbitone varied from day to day.

Preliminary experiments were performed to determine doses of β-tetra and M-P. β-tetra which did not affect the sleeping time of the anaesthetised mice in the absence of other drugs. The doses of these two compounds refer to the weights of the salts, hydrochloride and hydriodide respectively.

Means, standard errors and the significance of the differences between mean values were calculated for all experiments.

RESULTS

The results of experiments with β-tetra are shown in Table I, and those for M-P. β-tetra are shown in Table II.

5-HT increased the sleeping time of mice anaesthetised with hexobarbitone from 26·4 minutes to 52·5 minutes. This prolongation was not

TABLE II

THE EFFECT OF *N*-METHYL-*N*-PROPYL-β-TETRAHYDRONAPHTHYLAMINE HYDROBROMIDE UPON THE SLEEPING TIME DUE TO HEXOBARBITONE, POTENTIATED BY 5-HYDROXYTRYPTAMINE CREATININE SULPHATE (5-HT), RESERPINE AND IPRONIAZID
(Room temperature 22°)

Drug	Dose in mg./kg.	Route	Mean sleeping times Min. ± SE.	Difference in sleeping times Min. ± SE.	t_8
Hexobarbitone ..	100	I.P.	26·4 ± 2·9 (22)	26·0 ± 1·5	17·6
Hexobarbitone + 5-HT	100 30	I.P. I.P.	52·5 ± 5·0 (11)		not significant
Hexobarbitone + 5-HT + M-P. β-tetra	100 30 25	I.P. I.P.	47·7 ± 3·7 (9)		
Hexobarbitone ..	100	I.P.	22·3 ± 1·0 (10)	23·6 ± 3·6	6·5
Hexobarbitone + reserpine	100 1	I.P. I.P.	45·9 ± 4·9 (10)		not significant
Hexobarbitone + reserpine + M-P. β-tetra	100 1 25	I.P. I.P. I.P.	39·3 ± 6·3 (10)		
Hexobarbitone ..	100	I.P.	23·1 ± 1·0 (24)	73·7 ± 8·6	8·6
Hexobarbitone + iproniazid	100 20	I.P. I.P.	96·8 ± 13·0 (12)		not significant
Hexobarbitone + iproniazid + M-P. β-tetra	100 20 25	I.P. S.C. I.P.	76·3 ± 21·54 (11)		

See Table I for explanation of numerals in brackets and for interpretation of values appearing in column headed "difference in sleeping times". The *t*-test shows significant ($P > 0·001$) differences between the mean values compared, except where the words "not significant" appear. The experiment with M-P. β-tetra with each of the three potentiating agents were performed at the same time as the experiments with β-tetra which are shown in Table I.

altered significantly by M-P. β-tetra. β-Tetra reduced the sleeping time of mice treated with 5-HT to 26·0 minutes a value which was not significantly different from the control time of 26·4 minutes for hexobarbitone alone. In the doses used, neither β-tetra nor M-P. β-tetra when injected alone before hexobarbitone administration gave a value for sleeping time different from that of the hexobarbitone controls.

Reserpine also increased the sleeping time from the control value approximately twofold. β-Tetra antagonised this potentiation completely, reducing the sleeping time of reserpine treated mice to 25·6

minutes compared with the control value of 22·3 minutes. M-P. β-tetra did not reduce significantly the reserpine potentiation.

Iproniazid produced a fourfold increase in sleeping time of hexobarbitone treated mice. This was reduced to 40·6 minutes by β-tetra and this value differed significantly ($P > 0{\cdot}001$) from that obtained for the group receiving iproniazid alone. It appears that this compound does not completely antagonise the action of iproniazid. From Table II it will be seen that M-P. β-tetra has no effect on the iproniazid potentiation.

In a further experiment with iproniazid, when the dose of hexobarbitone was reduced to 90 mg./kg., iproniazid (18 mg./kg.) increased the sleeping time from 12·8 to 22 minutes. A small but significant ($P > 0{\cdot}001$) antagonism towards this potentiation was shown even by such a small dose of β-tetra as 1 mg./kg.

Discussion

The methyl-propyl derivative of β-tetrahydronaphthylamine while showing a specific anti-5-HT action on the rat uterus preparation fails to exhibit any action against the potentiation of hexobarbitone hypnosis in mice by 5-HT. These results provide a further example of the lack of parallelism between the central and plain muscle effects of 5-HT antagonists. The effect is the reverse of that seen with β-tetra, where the central effect predominates. The latter compound not only antagonises the action of 5-HT on the duration of hexobarbitone hypnosis, but is also effective against the enhancement produced by reserpine. In this respect β-tetra is similar to lysergic acid diethylamide (LSD). It differs, however, from LSD in that it also antagonises the actions of iproniazid which LSD does not[7].

β-Tetra is an extremely active pyretic drug[8]. We have found that M-P. β-tetra lacks this action. Lessin and Parkes[9] and Fastier, Speden and Waal[10] have found that many drugs which prolong sleeping time also lower body temperature. The possibility that the antagonism of the potentiation of sleeping time by drugs is associated with a pyretic effect is suggested by the present results and merits further investigation.

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