BLOCKADE OF 5-HYDROXYTRYPTAMINE ANTIDIURESIS IN RATS BY 2-BROMLYSERGIC ACID DIETHYLAMIDE TARTRATE AND 1-METHYL-LYSERGIC ACID BUTANOLAMIDE

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The effects of two lysergic acid derivatives, 2-bromlysergic acid diethylamide 'BOL 148' and 1-methyl-lysergic acid butanolamide 'UML 491' on the antidiuresis induced by 5-hydroxytryptamine '5-HT' has been studied in rats given a dose of 1 mg./kg. 5-HT subcutaneously. BOL 148, 5 mg./kg., and UML 491, 2·5 mg./kg., counteracted the induced antidiuresis. By contrast, the antidiuretic effect of posterior pituitary extract was not blocked or diminished by BOL 148 or by UML 491. BOL 148 and UML 491 alone did not have a diuretic or antidiuretic action.

5-HYDROXYTRYPTAMINE antagonists have been widely studied for their activity against various effects of the amine. The investigations on isolated smooth muscle preparations and the cardiovascular and respiratory systems have received the most attention (see, for example, Gaddum and Hameed, 1954; Outschoorn and Jacob, 1960; Venulet, 1961; Bunag and Walaszek, 1962).

The antagonism of 5-HT antidiuresis has attracted less interest. Dasgupta (1957) demonstrated that chlorpromazine antagonised the 5-HT-induced reduction of excretion. As chlorpromazine is an antagonist of 5-HT it was interesting to see if derivatives of lysergic acid acted similarly. The effects of BOL 148 and UML 491 on 5-HT antidiuresis are now reported.

MATERIALS AND METHOD

Seventy-two male white rats, 150 and 250 g., of a laboratory strain, fed with a standard diet and water *ad libitum*, were used. Food and water were withdrawn 12 hr. before the experiments. The rats were given a water load of 5 ml. of distilled water per 100 g. body weight through a stomach tube. They were kept 3 in a cage, the urine draining directly into a measuring cylinder below, and the volume recorded every 15 min. for 4 hr.

Rats which excreted less than 50 per cent of the water load in the first 100 min. were excluded from the experiments.

The drugs were given immediately after the water load: 5-HT as the creatinine sulphate 1 mg./kg. subcutaneously, BOL 148, 5 mg./kg. and UML 491, 2·5 mg./kg., intraperitoneally, posterior pituitary extract* 1 unit/kg. subcutaneously. Control groups received 0·9 per cent sodium chloride solution, 1 ml./kg., either s.c. or i.p. This had no influence on the urine excretion after the water load.

The room temperature varied between 16 and 18°. All experiments began at 9 a.m.

* Polfa.

RESULTS

The Influence of BOL 148 *and* UML 491 *on* 5-HT *Antidiuresis*

The arrangement of the experiments and the results are presented in Table I. The urine volume is expressed as a percentage of the water load.

TABLE I

URINE EXCRETION AFTER 5-HT ALONE AND WITH BOL 148 OR UML 491 GIVEN TO ANIMALS LOADED WITH WATER 5 ML./100 G.

Drug	Dose mg./kg.	Number of rats	Urine volume as percentage of the water load volume after			
			60 min.	120 min.	180 min.	240 min.
Control	–	18	41·0	71·8	80·4	83·2
5-HT	1	18	4·5	18·0	42·1	57·5
5-HT + BOL 148 ..	1 5	18	25·5	67·7	84·2	89·3
5-HT + UML 491 ..	1 2·5	18	31·4	62·3	76·4	80·2

The differences between the 5-HT group and the groups receiving 5-HT + BOL 148 and UML 491 are significant at the 5 per cent level.

Specificity of Antagonism

To prove the specificity of the antagonism of the 5-HT antidiuresis exerted by BOL 148 and UML 491, the experiments were repeated on the same rats using posterior pituitary extract given subcutaneously instead of 5-HT. The 5-HT antagonists have also been studied alone to ascertain whether they themselves have diuretic or antidiuretic properties. The relevant results are in Table II.

TABLE II

URINE EXCRETION AFTER BOL 148 OR UML 491 ALONE OR WITH POSTERIOR PITUITARY EXTRACT GIVEN TO ANIMALS LOADED WITH WATER 5 ML./100 G.

Drug	Dose mg./kg.	Number of rats	Urine volume as percentage of the water load volume after			
			60 min.	120 min.	180 min.	240 min.
BOL 148	5·0	12	32·4	73·5	84·0	88·8
UML 491	2·5	12	39·5	66·3	86·1	88·4
Post. pituitary extract	1 unit/kg.	12	14·1	22·1	36·1	41·7
Post. pituitary extract + BOL 148	1 unit/kg. 5·0	12	11·0	23·2	40·3	42·0
Post. pituitary extract + UML 491	1 unit/kg. 2·5	12	13·8	24·1	37·3	46·0

The volume of urine excreted at 240 min. showed a significant variation between the groups receiving posterior pituitary extract, posterior pituitary extract + BOL 148, posterior pituitary extract + UML 491 and the control group from Table I.

The results were also evaluated by calculating the point at which half of the total urine quantity was excreted, "the point of maximum excretion rate" (Burn, Finney and Goodwin, 1952). It was considered unnecessary to reject an "initial urine amount not belonging to the true period of

excretion", as recommended by Burn and others, if the urine bladder was previously emptied. The results are given in Table III.

TABLE III

THE POINT OF MAXIMUM RATE OF EXCRETION (MIN.) AFTER A WATER LOAD OF 5 ML./100 G.

Drugs	Dose mg./kg.	Point of maximum rate of excretion in different groups of 3 rats Average (min.)
Control	—	62·6 (54–71)
5-HT	1·0	149·7 (135–171)
5-HT + BOL 148	1·0	85·0 (71–95)
	5·0	
5-HT + UML 491	1·0	78·6 (70–94)
	2·5	
UML 491	2·5	66·2 (57–78)
BOL 148	5·0	74·2 (57–84)
Posterior pituitary extract	1 unit/kg.	112·7 (96–138)
Posterior pituitary extract + BOL 148	1 unit/kg.	106·7 (90–128)
	5·0	
Posterior pituitary extract + UML 491	1 unit/kg.	117·5 (91–135)
	2·5	

DISCUSSION

The data in Tables I and III show that in the hydrated rats a single injection of 5-HT, 1 mg./kg., causes a reduction of the urine excretion. A simultaneous intraperitoneal injection of BOL 148 or UML 491 inhibits or diminishes this antidiuretic action. This is evident both when comparing the hourly recorded urine volume in the groups and when estimating the points of maximum rate of excretion.

In considering how BOL 148 and UML 491 act against a 5-HT antidiuresis it is necessary to recall the theories of the mode of action of 5-HT on the kidneys. Erspamer (1956) first concluded that the 5-HT antidiuresis was due to preferential constriction of the afferent glomerular arterioles. Sala and Castegnaro (1953), on the other hand, believe that 5-HT is a water reabsorbing hormone. The vascular origin of the antidiuretic action of 5-HT was confirmed by Abrahams and Pickford (1956). Thus it seems probable that the lysergic acid derivatives abolish or diminish the antidiuretic response to 5-HT in the same manner as they prevent its cardiovascular effects.

The specifity of this action was investigated, and it was found that antidiuresis after posterior pituitary extract was not prevented by BOL 148 and UML 491. Neither BOL 148 nor UML 491 have significant diuretic or antidiuretic properties. Therefore it is concluded that their action on 5-HT antidiuresis is a specific one.

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