NATURE OF 5-HT RECEPTORS IN CENTRAL VASOMOTOR LOCI

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Gaddum and Hameed (1) were first to suggest that 5-hydroxytryptamine (5-HT) produces some of its effects by acting on specific receptors. Gaddum and Picarelli (2) established that the guinea pig ileum contains two types of 5-HT receptors, each being blocked by a separate set of blocking agents. The "nervous receptors" (M-receptors) were blocked by morphine, atropine, cocaine and methadone; the other type, the "smooth muscle receptors" (D-receptors) were blocked by dibenzylamine, dihydroergotamine and 5-benzoyloxygramine. Since then the nature of 5-HT receptors in various organs of the body has been worked out. However, studies on the nature of 5-HT receptors and the effect of various antagonists on the effects of 5-HT in the central nervous system are few. In the present study an attempt has been made to work out the nature of the receptors involved in the central hypotensive response of 5-HT administered in the lateral cerebral ventricle of dogs (3). A preliminary report of this work has already been published (4).

METHODS

The data were obtained from 25 adult mongrel dogs of either sex anesthetised with 30 mg/kg pentobarbital sodium given intravenously, bilaterally vagotomised and maintained on positive pressure artificial respiration. The blood pressure was recorded from a common carotid artery by means of a mercury manometer on a smoked paper. The drugs, dibenzylamine hydrochloride, 5-hydroxytryptamine creatinine sulphate and morphine hydrochloride were dissolved in 0.5 ml of normal saline and were administered through a polythene cannula placed in lateral cerebral ventricle according to the technique of Bhargava and Tangri (3). The reactivity of the vasomotor center was judged by the pressor response obtained by the bilateral occlusion of the common carotid arteries for 30 seconds. In addition the effect of the drugs on the blood pressure level was also noted. The significance of the change in the blood pressure level and the height of the carotid occlusion response induced by a drug was determined by student's 't' test ($P=0.05$).

RESULTS

The results obtained in the present investigation are summarized in Table 1.

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TABLE 1. Effect of 5-HT on blood pressure and carotid occlusion response in normal and morphine or dibenzylidine treated dogs.

All drugs administered into the lateral cerebral ventricle. Values along with the standard errors are given. (*) indicates significant change from the control value ($P=0.05$). C.O.=Carotid occlusion response.

Drug	No. of dogs	Control		After drug administration		Time of peak effect (min)
		Mean B.P. level (mmHg)	Mean C.O. (mmHg)	Mean B.P. level (mmHg)	Mean C.O. (mmHg)	
5-HT						
(a) 1 mg	5	127± 5.6	38±2.6	83±14.7*	14± 4.5*	17±4.2
(b) 1 mg (2 hr after a)	3	132± 3.5	33±5.8	131± 9.0	30± 5.1	27±3.3
Morphine						
10 mg	9	132± 7.4	40±4.9	137± 7.3	40± 5.3	17±1.8
Dibenzyline						
5 mg	9	132± 3.6	40±3.1	147± 6.6	50± 6.6	22±2.3
5-HT						
(a) 1 mg (20 min after morphine pretreatment)	3	137± 1.7	44±7.4	119± 8.5	33± 5.5	31±5.8
(b) 1 mg (2 hr after a)	2	128±70.0	34±0.0	65±23.9*	13± 9.2*	98±5.3
(c) 1 mg (2 hr after b)	2	125±10.7	36±7.3	129± 7.9	33± 5.0	25±3.6
Morphine						
10 mg (30 min after 5-HT)	3	81±14.1	11±5.1	132± 9.7*	55±10.0*	28±4.0
5-HT						
1 mg (25 min after dibenzyline pretreatment)	6	143±11.4	44±4.4	131±16.2	31± 6.0	23±2.6

Effect of 5-HT

5-HT (1 mg) administered in the lateral cerebral ventricle in dogs produced a marked fall in blood pressure and considerable reduction in carotid occlusion response. The effect lasted for about 1½ hours (85±13.2 minutes). Repetition of this dose after two hours, when blood pressure and carotid occlusion response had almost recovered, failed to elicit a significant response.

Effect of morphine and dibenzylidine

Intracerebroventricular administration of morphine (10 mg) or dibenzylidine (5 mg) produced an insignificant increase in blood pressure and in the height of the carotid occlusion response.

Morphine 5-HT interaction

Administration of 5-HT (1 mg) 20 minutes after the administration of 10 mg of

morphine failed to elicit significant fall of blood pressure and diminution of the carotid occlusion response. In 2 experiments, repetition of this dose of 5-HT after two hours, when the effect of morphine had passed off, resulted in the characteristic fall of blood pressure and reduction of the carotid occlusion response. However, administration of the same dose of 5-HT for the third time, two hours after the second dose, was without any effect.

In three experiments morphine was administered 30 minutes after the administration of 5-HT and it rapidly restored the blood pressure level and carotid occlusion response which had been reduced by 5-HT. The increase in blood pressure and carotid occlusion response produced by morphine in these animals was significant.

Dibenzylamine 5-HT Interaction

Administration of 1 mg of 5-HT, 25 minutes after the administration of 5 mg of dibenzylamine failed to elicit significant decrease of blood pressure and carotid occlusion response.

DISCUSSION

5-HT administered parentally does not cross the blood-brain barrier in most of the species and so does not produce characteristic changes in the functions of the central nervous system. Due to this difficulty, the nature of 5-HT receptors present there has not been adequately worked out. Gaddum and Vogt (5) found that both morphine and LSD which block different types of 5-HT receptors in the periphery were effective in blocking the 5-HT induced CNS depression in cats. On the other hand, Tedeschi, Tedeschi and Fellows (6) observed that LSD but not morphine could block the convulsions induced in rats by tryptamine which acts on 5-HT receptors.

Bhargava and Tangri (3) observed that 5-HT administered into the lateral cerebral ventricle of the dog produces a hypotensive response. In the present study it was planned to determine the nature of 5-HT receptors in the central vasomotor loci by observing the effect of 5-HT antagonists on this response. The 5-HT antagonists employed were morphine and dibenzylamine which block M and D type of receptors respectively in the periphery.

It is easy to judge the efficacy of an antagonist by eliciting a response to the agonist before and after the administration of antagonist. This was not possible in the present study since the administration of second dose of 5-HT produced hardly any effect in normal animals. The effect of 5-HT was, therefore, observed in normal as well as in morphine or dibenzylamine pretreated dogs. Neither morphine nor dibenzylamine by themselves produced a significant change in blood pressure level and the height of the carotid occlusion response.

It was observed that 5-HT produced a significant fall in blood pressure and diminution of carotid occlusion response in normal dogs but not in the dogs pretreated with morphine or dibenzylamine. Thus morphine as well as dibenzylamine are capable of blocking the central hypotensive response of 5-HT. It, therefore, appears that 5-HT receptors in the central vasomotor loci are neither of M type nor of D type but are of an undifferen-

tiated nature which are blocked by both M as well as D receptor blocking agents.

It is interesting to note that when first dose of 5-HT failed to produce a hypotensive effect in dogs pretreated with morphine, second dose of 5-HT after 2 hours produced characteristic hypotensive response and the third dose did not produce any effect. This is in contrast to the findings in normal dogs in which second dose of 5-HT is almost ineffective. It appears that in the presence of morphine, 5-HT is ineffective and tachyphylaxis does not develop to its subsequent administration. It develops only when a dose of 5-HT has produced the hypotensive effect.

SUMMARY

5-HT produced a significant decrease of blood pressure and carotid occlusion response when administered into the lateral cerebral ventricle of normal dogs but not in dogs pretreated with morphine or dibenzylamine. It is concluded that 5-HT receptors in the central vasomotor loci are neither of M-type nor of D-type but are of an undifferentiated nature which are blocked by both M as well as D-receptor blocking agents.

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