ANALYSIS OF CENTRAL SEROTONINERGIC STRUCTURES OF THE GLOSSOMANDIBULAR REFLEX

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The D-serotonin antagonist mexamine (5-methoxytryptamine, 2 mg/kg) and the universal antagonist proguanil (25 mg/kg) are selective antagonists, whereas in relation to 6-methoxytryptamine, dihydroergotamine, chlorpromazine, and trifluoperazine, they do not inhibit manifestation of the depressant action of adrenalin and acetylcholine on the glossomandibular reflex. The central serotonin-negative effect of the phenothiazine derivatives is dependent on their penetration through the blood-brain barrier.

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In a previous study [1] we showed that, except chlorpromazine, none of the serotonin antagonists blocks the serotoninergic structures of the glossomandibular reflex in doses effective in their action on peripheral receptors.

The object of the present investigation was to study whether depression of the central serotonin action takes place if the effective doses of certain antagonists are increased from 2 to 5 times.

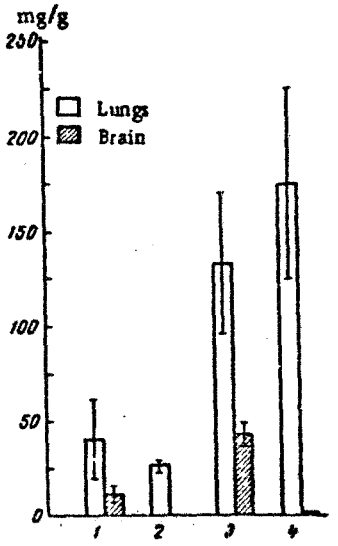

Fig. 1. Distribution of some phenothiazine derivatives in lungs and brain stem of cats 2 min after intravenous injection of preparations. 1) chlorpromazine (2 mg/kg); 2) trifluoperazine (1 mg/kg); 3) trifluoperazine (5 mg/kg); 4) dixyrazine (5 mg/kg).

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with chloralose (80 mg/kg), intravenously). The effect of the drugs on D-serotoninergic structures of the pulmonary vessels and the glossomandibular reflex was investigated by methods described previously [1]. To analyze the central serotoninergic structures, various serotonin antagonists were used (their names, the character of their action, doses, and mode of administration are indicated in Table 1).

Quantitative estimation of the phenothiazines in the lungs and brain stem was carried out spectrophotometrically by a slightly modified method of Wechsler and Forrest [5]. The substances were extracted from the tissues 2 min after intravenous injection, when the phenothiazines were present in the body in an unchanged form. It was therefore considered that the stage of conversion of the extracted compounds into oxidized products could be omitted.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that M-antagonists, even in large doses, had no effect on the ability of serotonin to block the glossomandibular reflex. However, D-antagonists definitely diminished the central serotonin effect. Proguanil, a universal antagonist with a marked D-serotonin-negative component also proved to be active (Table 1).

The antiserotonin action of 5-methoxytryptamine and proguanil is evidently specific, because the depriming effects of adrenalin and acetylcholine on the glossomandibular reflex was not abolished by these substances. The results obtained suggest that, in their sensitivity to blocking agents, the

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TABLE 1. Effect of Peripheral Serotonin Antagonists on Ability of Serotonin, Adrenalin, and Acetylcholine to Depress the Glossomandibular Reflex

Classification of serotonin antagonists	Name of preparation	Dose (in mg/kg, intravenously)	Depression of reflex (in percent)					
			serotonin (200 μg/kg, intravenously)		adrenalin (100 μg/kg, intravenously)		acetylcholine (15 μg/kg, into carotid artery)	
			before administration of preparation	2 min after administration of preparation	before administration of preparation	2 min after administration of preparation	before administration of preparation	2 min after administration of preparation
M-antagonists	Morphine	5	40.2±3.4	43.5±10.9				
	Procaine	10	28.3±5.3	20.5±4.9				
	Atropine	5	55.5±9.3	46.7±8.9				
Universal antagonists	Isoprenaline	5	31.8±5.3	37.3±7.3				
	Dixyrazine	5	44.5±5.4	42.6±3.5				
	Trifluoperazine	1	59.0±11.9	70.6±12.6				
	"	5	34.4±7.8	21.2±5.5[2]	54.1±14.2	37.7±10.4[2]		
	Chlorpromazine[1]	2	62.4±11.9	50.3±9.1[2]	30.1±7.1	13.8±6.8[2]		
	Proguanil	25	33.8±5.2	14.9±3.6[2]	32.2±6.7	41.8±14.6	37.3±3.1	35.1±3.24
D-antagonists	5-methoxytryptamine	2	21.3±6.6	12.5±5.0[2]	33.3±11.2	37.1±10.7	30.2±9.8	46.6±7.7
	Dihydroergotamine	5	46.9±1.6	19.1±6.8[2]	51.1±7.7	27.6±5.6[2]		
	6-methoxytryptamine	6	60.0±7.7	39.6±6.7[2]	63.1±6.3	37.5±7.9[2]		

[1] In experiments with adrenalin, chlorpromazine was given in a dose of 1 mg/kg.
[2] $P < 0.05$.

central serotoninergic structures of the glossomandibular reflex are probably similar to the peripheral D-structures.

The absence of effect of many peripheral serotonin antagonists in effective doses on central serotoninergic structures is therefore probably due not to qualitative differences between peripheral and central serotonin receptors but to inadequate penetration of the antagonists into the brain. To prove this point, the antiserotonin effect of certain phenothiazine derivatives was compared with their distribution in the brain and peripheral tissue.

We used chlorpromazine (2 mg/kg), trifluoperazine (1 mg/kg), and dixyrazine (5 mg/kg). In these doses the preparations inhibited the D-structures of the pulmonary vessels almost equally (by 94.8±4.7%, $P < 0.001$; 89.3±4.2%, $P < 0.001$; and 92.4±9.3%, $P < 0.001$; respectively). However, only chlorpromazine exhibited a central antiserotonin effect. The antiserotonin action of the phenothiazines corresponded completely to their distribution in the tissues: all preparations were found in large concentrations in the lung tissue, but only chlorpromazine was found in the brain stem. When the dose of trifluoperazine was increased 5 times it exhibited definite central antiserotonin properties, and at the same time was detected in large concentrations in the brain stem (Fig. 1).

The results described above suggest that one cause of the absence of antiserotonin effects in some of the phenothiazines is their limited ability to penetrate through the blood-brain barrier. This evidently applies also to other peripheral D-antagonists of serotonin, which do not possess central antiserotonin properties.

The blood-brain barrier evidently prevents free penetration of M-antagonists of serotonin into the central nervous system also. However, it is difficult to explain the absence of a central antiserotonin effect of, for example, morphine and procaine, in this way because these substances in the doses which we

used have a definite central action and evidently penetrate into the brain in sufficient quantities [2–4, 6, 7]. The impression is thus created that the central serotoninergic structures of the glossomandibular reflex are insensitive to the action of M-antagonists.

It can thus be concluded from the results of this investigation that the central serotonin structures of the glossomandibular reflex probably belong to the D-types of serotonin receptors.

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