PHARMACOLOGICAL CHARACTERISTICS OF SEROTONINERGIC STRUCTURES OF THE LUNGS RESPONSIBLE FOR THE RESPIRATORY CHEMOREFLEX TO SEROTONIN

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Experiments on cats showed that the serotoninergic structures of the lungs responsible for reflex apnea to serotonin are similar in their sensitivity to blocking agents (lysergic acid derivatives, cyproheptadine, morphine, tipindole) to T-structures responsible for coronary and depressive pulmonary chemoreflexes, and differ from D- and M-serotoninergic structures of the smooth muscles and autonomic ganglia.

The authors have shown previously that serotoninergic structures responsible for coronary and depressor pulmonary chemoreflexes* differ significantly from structures of the D- and M-type in their resistance to lysergic acid derivatives and in their high sensitivity to tipindole, on account of which they have been called key-serotoninergic structures [2-4]. Serotonin, if injected intravenously into cats, causes not only reflex bradycardia and hypotension, but also respiratory arrest [6, 15, 16]. After intravenous injection of serotonin in doses up to 50 μg/kg the respiratory arrest is mainly the result of a reflex from receptors of the lungs. The afferent pathway of this reflex, like that of the coronary and depressor pulmonary reflex, runs in the vagus nerves. It is still undecided whether the respiratory and depressor pulmonary chemoreflexes arise from the same or different nerve endings [7, 13], and the possible identity of the serotoninergic structures responsible for these chemoreflexes remains virtually unstudied.

The object of the investigation described below was to study the effect of antagonists of D-, M-, and T-types on the apnea induced by serotonin. Besides the antagonists, the serotonin agonist α-naphthyldiguanide was used to determine the pharmacological properties of the structures.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). All substances were injected intravenously. The dose of serotonin was so chosen that the original period of respiratory arrest was 10-25 sec. Usually, a dose of 20-50 μg/kg serotonin was required to obtain this effect. Larger doses were not used because, if they are, the nonreflex component of the respiratory response is clearly visible [8]. Respiration was recorded on the smoked drum of a kymograph by means of a Marey's capsule. The total number of experiments was 60.

* Coronary and depressor pulmonary chemoreflexes arise from receptors of the heart and lungs and are exhibited as bradycardia and hypotension [7].

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TABLE 1. Effect of Serotonin Antagonists of D-, M-, and T-types on Respiratory Pulmonary Chemoreflex to Serotonin

Antagonist	Dose (in mg/kg)	No. of expts.	Change in duration of reflex apnea (in % of initial level)
Cyproheptadine	0,2	6	—5 (—14 to +4)
Lysenyl	0,03	5	+32 (—8 to +72)
	0,4	5	+96 (+51 to +141)
Morphine	1,0	6	+1,6 (—12 to 15,2)
	2,0	6	—3 (—10 to +4)
Tipindole	0,5	5	—46 (—22 to —68)
	1,0	7	100

Note. Significant differences shown in parentheses. Changes in duration of apnea during period of maximal antiserotonin activity of antagonists are shown in the last column: 30 min after injection of cyproheptadine and 1 h after injection of lysenyl.

EXPERIMENTAL RESULTS AND DISCUSSION

Cyproheptadine, a serotonin antagonist of the D-type, when given intravenously in doses of 100-200 μg/kg, adequate for producing blocking of D-serotoninergic structures [17], had no definite effect on the serotonin apnea for 3-4 h after injection (Table 1). The lysergic acid derivative lysenyl, in doses of 20-500 μg/kg, close to the maximal limit of tolerance, caused no change in or increased the duration of the reflex apnea induced by serotonin. At the same time lysenyl inhibits D-serotoninergic structures, notably the myotropic component of serotonin-induced bronchospasm, in doses of 20-30 μg/kg [4, 14, 19]. Bronchospasm to serotonin is inhibited also by LSD-25 in the same doses [12, 14]. Meanwhile LSD-25 in doses up to 500 μg/kg, according to results of experiments by the writers themselves and by Gyermek and Sami [11], increases the duration of serotonin-induced apnea. The serotoninergic structures responsible for the respiratory chemoreflex to serotonin from the receptors of the lungs thus differ significantly in their sensitivity to blocking agents from structures of the D-type.

The results of the present experiment showed that morphine, an antagonist of M-type, in doses of 1-2 mg/kg intravenously did not inhibit the reflex apnea induced by serotonin (serotonin was injected 1, 5, and 20 min and 1 h after the morphine). Structures of M-type are known to be blocked in cats by morphine in doses of 0.2-0.5 mg/kg [18]. Consequently, the serotoninergic structures responsible for apnea differ from structures of the M-type.

Tipindole in a dose of 1 mg/kg, in which it competitively blocks serotoninergic structures of the T-type, responsible for the depressor pulmonary and coronary chemoreflexes to serotonin, but has no appreciable effect on structures of the M- and D-type [2, 5], inhibited the reflex apnea to serotonin in all experiments (Table 1).

Hence, the serotoninergic structures responsible for the respiratory pulmonary chemoreflex to serotonin differ from structures of the D- and M-types and are similar to structures of the T-type responsible for the depressor pulmonary and coronary chemoreflexes. This conclusion was also confirmed by the results of experiments with α-naphthyldiguanide. Derivatives of guanidine and diguanide are known to have no effect on serotoninergic structures of the D-type, although they are antagonists of serotonin in relation to structures of M- and T-types [2, 9, 10]. In these experiments α-naphthyldiguanide induced apnea in doses of 10-20 μg/kg. The appearance of a respiratory chemoreflex to guanidine does not involve excitation of structures of the M-type, for according to Ivanova [1], this chemoreflex is not inhibited by morphine or trimeperidine in doses of 1-2 mg/kg. At the same time, in the present experiments tipindole, in a dose of 1 mg/kg, caused total inhibition of the respiratory reflex to α-naphthyldiguanide. Comparison of the doses in which tipindole doubled the threshold of reflex bradycardia and reflex apnea to α-naphthyldiguanide revealed no significant difference: the first was 0.4 (0.43-0.37) mg/kg, the second 0.46 (0.62-0.29) mg/kg. Similar results were also obtained as regards the doses of tipindole which doubled the threshold of the reflex responses to serotonin.

The results are evidence in support of the identity of the structures responsible for the respiratory chemoreflex to serotonin and structures of the T-type responsible for the depressor pulmonary and coronary chemoreflexes. This does not, of course, rule out the possibility that the serotoninergic structures of similar nature are connected in the case of the pulmonary chemoreflex with some sensory nerve endings, and in the case of the depressor pulmonary reflex, with other nerve endings. It can be concluded from the facts described above that the reflex apnea to serotonin is not due to bronchospasm, as Dawes and Comroe [7] suggested. In fact, bronchospasm to serotonin is inhibited by lysergic acid derivatives in doses of 20-30 μg/kg, while the apnea is intensified under these conditions; at the same time, tipindole inhibits apnea in doses of 0.4-1.0 mg/kg, while bronchospasm is reduced by injection of tipindole only in a dose of 5 mg/kg [5]. The difference between the serotoninergic structures responsible for the respiratory chemoreflex and structures of the D- and M-types evidently suggest that this reflex is not a result of the other myotropic and ganglionic effects of serotonin.

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