NATURE OF CENTRAL ADRENERGIC AND SEROTONIN-SENSITIVE STRUCTURES CONCERNED IN THE FACILITATORY EFFECT OF BIOAMINES ON THE AMMONIA REFLEX

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The duration of the reflex apnea produced in cats by stimulation of the upper respiratory tract with ammonia increases following injection of noradrenalin and serotonin into the cerebral ventricles, and also following intraperitoneal injection of dihydroxyphenylalanine and 5-hydroxytryptophan. The effect of noradrenalin was abolished by phentolamine, and that of serotonin by morphine.

The neurochemical mechanisms of function of respiratory neurons have received little study. The use of microelectrode techniques and histochemical methods in recent years have revealed the presence of neurons sensitive to dopamine, serotonin, and noradrenalin in nuclei of the vagus nerve, the tractus solitarius, the ventrolateral zone of the caudal divisions of the medulla, and reticular neurons of the pons [9-11, 14, 18]. These results suggest participation of bioamines in the mechanism of function of the bulbar respiratory center [1, 5, 7, 8], which lies in the reticular formation of the brain stem [2-4]. However, no data yet exist regarding the nature of adrenergic and serotonin-sensitive structures of the respiratory neurons.

The object of the present investigation was to study the effect of bioamines and their precursors on the inhibitory respiratory reflex produced by stimulation of the upper respiratory tract by ammonia, and also to study the mechanism of onset of this effect.

EXPERIMENTAL METHOD

Experiments were carried out on 65 cats weighing from 1.9 to 3.5 kg, anesthetized with uretane (800 mg/kg, intraperitoneally). Respiration was recorded by means of a Marey's capsule and cannula introduced into the trachea. The functional state of the central components of the inhibitory reflex evoked by stimulation of the nasal mucosa with ammonia was judged from the presence of a respiratorypause [3]. This was evoked by a method which allowed application of strictly local stimuli, of measured strength, which was maintained throughout the experiment, for short periods (1.5 sec). In the course of the experiment the reflexogenic zone was stimulated not more than 12 times at intervals of 5-10 min. To assess the respiratory reflex quantitatively, changes in the duration of reflex apnea produced by monoamines were determined. In two series of experiments, 4 h before the experiment began the animals received an intraperitoneal injection of dihydroxyphenylalanine (DHPA) and 5-hydroxytrytophan (5-HTP) in a dose of 50 mg/kg. Noradrenalin (NA) and serotonin (5-HT) were injected into the lateral ventricle through a permanent cannula [12]. To analyze receptor structures of the trigemino-bulbar pathways in the brain stem through which specific effects of NA and 5-HT are transmitted, dihydroergotamine (DET), a specific antagonist of the α-effects of catecholamines [15] and the D-effects of serotonin [13], the α-adrenolytic phentolamine [15, 16], the β-adrenolytic propranolol [7], and morphine, which inhibits effects due to the action of 5-HT on serotonin-

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TABLE 1. Effect of Bioamines and Their Precursors on Duration of Reflex Apnea

Concn. of ammonia (in %)	Duration of reflex apnea (in sec)					
	intraperitoneal injection			intraventricular injection		
	control	DHPA	5-HTP	control	NA	5-HT
1,25	2,03 1,21—2,85	5,33 3,58—7,08	4,28 2,53—6,03	3,02 2,35—3,69	5,37 4,07—6,67	5,62 4,04—7,2
2,5	3,24 2,68—3,8	6,82 5,41—8,23	5,56 3,9—7,22	4,68 4,18—5,18	8,12 6,37—9,87	8,15 6,68—9,62
5	5,73 4,22—7,24	8,3 7,03—9,57	7,88 6,86—8,8	6,5 5,23—7,77	11,25 8,09—14,41	11,18 7,58—14,78

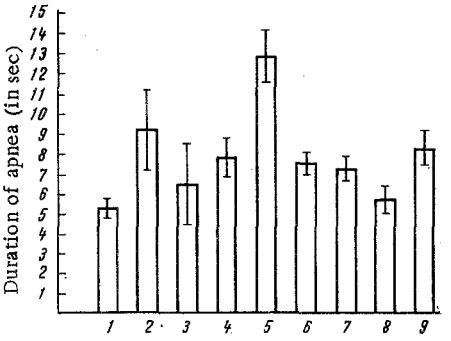

Fig. 1. Effect of phentolamine, propranolol, dihydroergotamine, and morphine, injected into the lateral ventricle, on the increase, caused by bioamines, in the duration of reflex apnea in response to stimulation of the nasal mucosa by 2.5% ammonia: 1) duration of reflex apnea produced by ammonia; 2) ditto, after injection of noradrenalin; 3) ditto, after injection of noradrenalin against the background of phentolamine; 4) ditto, after injection of noradrenalin, against the background of propranolol; 5) ditto, after injection of noradrenalin against the background of morphine; 6) ditto, after injection of serotonin; 7) ditto, after injection of serotonin against the background of dihydroergotamine; 8) ditto, after injection of serotonin against the background of morphine; 9) ditto, after injection of serotonin against the background of phentolamine (values of M ± m given).

sensitive structures of the M-type [13], were injected into the ventricle 10 min before injection of the amines. The bioamines and their antagonists were injected in a dose of 200 μg (calculated as base) in a volume of 0.25 ml.

RESULTS AND DISCUSSION

Stimulation of the nasal mucosa with ammonia (1.25, 2.5, and 5%) evoked an inhibitory respiratory response in all experiments, manifested by holding the breath for a few seconds followed by resumption of respiratory movements. The reflex holding of the breath takes the form of an expiratory pause, its duration depending on the concentration of ammonia used. The afferent structure concerned in this reflex is the trigeminal nerve, along which impulses reach the brain stem at the level of the tegmentum of the pons [3].

Further experiments showed that preliminary injection of DHPA and 5-HTP significantly increased the duration of the respiratory pause produced by stimulation of the nasal mucosa with ammonia. A similar effect was produced by NA and 5-HT when injected into the lateral ventricle (Table 1).

The increase in the duration of reflex apnea due to NA was abolished by phentolamine, but not by propranolol. On the other hand, the analogous effect of 5-HT on the respiratory reflexes due to stimulation by ammonia (2.5%) was not affected by DET or phentolamine. Meanwhile, after preliminary injection of morphine, the increase in duration of reflex apnea usually evoked by serotonin did not take place (Fig. 1).

The ability of bioamines and their precursors to increase the duration of reflex apnea may be evidence that these substances act upon inhibitory neurons of the trigemino-bulbar pathways of the brainstem, through which the ammonia reflex is realized. This hypothesis is in agreement with the results of experiments confirming that such neurons exist in the system of the respiratory center [2, 4, 17]. However, despite the similarity between the external manifestations of the respiratory responses, the neurochemical mechanisms producing the observed effects of monoamines are not identical. Judging from the influence of phentolamine and propranolol on the NA effects, the increase in duration of reflex apnea produced by the amine is brought about through participation of α-adrenergic receptors. Experiments in which the inhibitory influence of α-adrenolytics on the inhibitory effects produced by direct stimulation of the reticular formation was established confirm the above argument [1]. Conversely, strengthening of the inhibitory respiratory responses by serotonin was unconnected with the action of the amine on α-adrenergic or D-serotonin receptors becuase it was unchanged by the action of phentolamine and DET. On the other hand, blocking of serotonin-sensitive structures of the M-type by morphine abolishes the increase in duration of the

respiratory pause produced by 5-HT. The observed antagonism is specific because the analogous effect of NA on the respiratory reflexes was not weakened but, on the contrary, was strengthened by morphine (Fig. 1).

It can be concluded from these results that the effect of 5-HT on the central components of the inhibitory respiratory reflex is associated with the action of the amine on serotonin-sensitive structures of the M-type. This conclusion correlates with the results of experiments showing that morphine depresses various types of inhibition in the central nervous system, including descending inhibitory influences arising during stimulation of the reticular formation [1].

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