IMPORTANCE OF CHOLINERGIC MEDIATION IN THE CENTRAL REGULATION OF RESPIRATION

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During local stimulation of various medullary structures, differences in the sensitivity of respiratory responses to methyldiazine were observed. The results indicate differences in the neurochemical organization of the central regulation of respiration and differences in the degree of participation of cholinergic mediation in these processes.

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There is no general agreement at the present time regarding the role of acetylcholine in the central regulation of respiration [1, 2, 6, 11-15].

The object of the present investigation was to examine the role of cholinergic mediation in the formation of respiratory responses in different parts of the bulbar respiratory center by studying the action of the central cholinolytic drug methyldiazine [8].

EXPERIMENTAL METHOD

Respiratory responses to local stimulation of various medullary structures were recorded in acute experiments on cats. The method used previously [3] was modified so that two electrodes, fixed into one holder connected to the micromanipulator, were inserted simultaneously into the floor of the 4th ventricle, so that their position could be adjusted vertically in stages with an accuracy of up to 50 μ. Stimulation was applied alternately through each electrode. At the end of the experiment the upper and lower points of stimulation were destroyed electrolytically through the stimulating electrodes. Brain sections were stained by Nissl's method and the location of the stimulated points reproduced in accordance with the atlas of the cat's medulla [7]. The pneumogram was recorded by means of a cannula, fixed into the pleural cavity. The arterial pressure was recorded in the femoral artery.

The physiological characteristics of the respiratory response were determined from the threshold voltage of stimulating current evoking a response, the type of response, and its change during a stepwise increase in the intensity of stimulation. To judge whether the stimulated point belonged to the respiratory center or not, changes in arterial pressure were recorded simultaneously. Responses before and after intravenous injection of one or two doses (0.1-5 mg/kg) of methyldiazine were determined in the same animal. Control experiments showed that responses arising at a given point during displacement of the electrodes in the dorso-ventral direction and vice versa were identical to those obtained at the first determination.

EXPERIMENTAL RESULTS AND DISCUSSION

Characteristic respiratory (expiratory or inspiratory) and vascular (pressor or depressor) responses appeared during stimulation of large areas of the floor of the 4th ventricle. Both respiratory and vascular responses could arise during stimulation of the same point. It was impossible to distinguish between the zones responsible for each response. The responses from different morphological zones were essentially indistinguishable in their threshold of excitability (apart from the zone of the tractus solitarius and nucleus ambiguus), or in the external manifestation of their response. Fundamental differences in the functional organization of different elements of the respiratory center have been clearly revealed by pharmacological investigations [4,5,9].

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TABLE 1. Effect of Methyldiazine on Respiratory Responses to Stimulation of Different Medullary Structures

Name of structure	Character of change in response produced by methyldiazine	Frequency of recorded responses	
		expiration	inspiration
Parvocellular reticular nucleus and zone of nucleus of tractus solitarius	Suppression	13	–
	Strengthening	–	15
Gigantocellular reticular nucleus	Suppression	–	–
	Strengthening	19	10
Ventral reticular nucleus	Suppression	2	–
	Strengthening	6	6
	No change	–	23

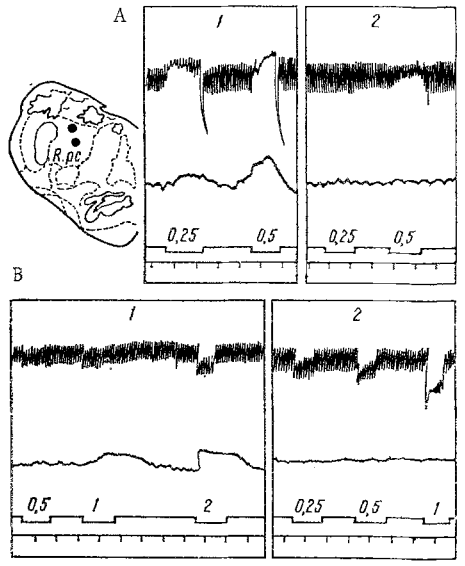

Fig. 1. Effect of methyldiazine on vascular and expiratory (A) and inspiratroy (B) respiratory responses to stimulation of the parvocellular reticular nucleus (R.pc): 1) before injection of methyldiazine; 2) after injection of 0.5 mg/kg methyldiazine. From top to bottom: respiration; arterial pressure; marker of stimulation (in V); time marker, 10 sec. Localization of stimulating electrodes shown on diagram of section through medulla.

In the present investigation, methyldiazine had different effects on respiratory responses to stimulation of different medullary structures (Table 1).

Expiratory responses evoked by stimulation of the parvocellular reticular nucleus and zone of the nucleus of the tractus solitarius were suppressed by methyldiazine. The phase shift of respiration was reduced, and a higher intensity of stimulation was required to obtain a response (Fig. 1A). The expiratory apnea developing in the period of stimulation was often replaced in the control experiments by maximal inspiration immediately after the cessation of stimulation, indicating the presence of active inhibition of inspiratory mechanisms during stimulation (the "rebound" phenomenon). During the action of methyldiazine, the rebound phenomenon disappeared completely. Conversely, the inspiratory responses to stimulation of the same structures were strengthened by the action of methyldiazine (Fig. 1B). Despite the fact that the changes in the respiratory responses were in different directions, the changes in arterial pressure were uniformly inhibited by methyldiazine in all cases of stimulation of the parvocellular nucleus and the nucleus of the tractus solitarius (Fig. 1A, B).

Respiratory (expiratory and inspiratory) responses to stimulation of the gigantocellular nucleus were strengthened by methyldiazine. The amplitude of the phase shift was increased, and a lower intensity of stimulation was required to produce the maximal response. A decrease in the amplitude of background respiration, accompanying the respiratory responses, and a slowing (in expiratory) or quickening of respiration (during inspiratory responses) took place under the influence of methyldiazine at lower strengths of stimulation, and were more marked (Fig. 2A). During expiratory responses, methyldiazine led to the appearance of a "rebound" phenomenon.

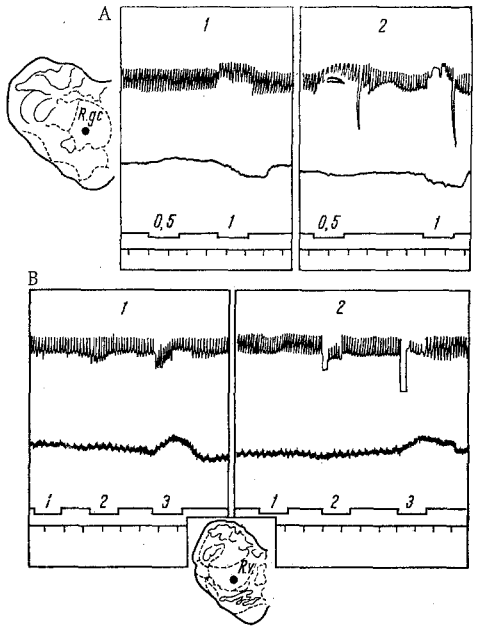

Fig. 2. Effect of methyldiazine on respiratory and vascular responses to stimulation of gigantocellular (A) and ventral (B) reticular nuclei (R.gc and R. v, respectively): 1) before injection of methyldiazine; 2) after injection of 0.5 mg/kg methyldiazine. Remainder of legend as in Fig. 1.

The effects of methyldiazine on respiratory responses to stimulation of the ventral reticular nucleus were inconstant. In most cases the inspiratory responses were unchanged and the expiratory were strengthened. In some experiments, the inspiratory responses were strengthened (Fig. 2B). Methyldiazine also had an inconstant effect on the vascular responses obtained from these structures. However, no parallel was observed in this case also: inhibition of vascular responses could be accompanied by strengthening of respiratory, and vice versa. These facts indicate definite differences in the neurochemical organization of the central mechanisms of regulation of respiration and of vascular tone.

The effect of the cholinolytic drug methyldiazine on respiratory responses to stimulation of different medullary structures thus at times differs in its essential principles. These results support the previous hypothesis [5] that systems participating in the central regulation of respiration differ in their neurochemical organization. The decrease in amplitude of expiratory responses and suppression of the rebound phenomenon observed during stimulation of the parvocellular nucleus and nucleus of the tractus solitarius observed under the influence of methyldiazine may be associated with inhibition of "anti-inspiratory" neurons [6] and hence, to the disturbance of inhibitory mechanisms. This suggestion concerning the cholinergic nature of these respiratory zones agrees perfectly with the histochemical data indicating clustering of neurons containing a higher concentration of cholinesterase in the region of the tractus solitarius and the lateral nuclei which surround it [10]. Since the medial portions of the reticular formation contain effector neurons whose activity is under the influence of "primary" neurons of the lateral nuclei [4, 7], the potentiation by methyldiazine of respiratory responses to stimulation of the gigantocellular, and in some cases, the ventral nucleus in these experiments can also be regarded as deinhibition resulting from suppression of the "primary" expiratory ("anti-inspiratory") neurons. In most of the present experiments, changes in maximal inspiratory or expiratory respiratory responses were observed without any significant change in the background respiration under the influence of methyldiazine. These facts indicate not merely differences in the importance of cholinergic mediation in the activity of particular respiratory zones, and, evidently, in the degree of participation of these structures in the nervous regulation of respiration, but also that changes in respiration toward expiration or inspiration, as well as background respiration itself, are coordinated by different and independent mechanisms.

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