ON THE CAUSES OF AUTOMATIC EXCITATION OF THE FROG RESPIRATORY CENTER

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The difficulty in elucidating the reasons underlying the generation of automatic excitation in the respiratory center of higher vertebrates is partially explained by the presence of the large number of connections which this vital center has established to ensure the regulation of oxygen supply in the lungs over the course of evolution. This is why investigators work with animals belonging to an early stage of evolution, with simpler principles in the schema for the structure and physiological mechanism of activity of their respiratory center. In connection with this, great interest is aroused by the well known fact that the frog's respiration is completely suppressed when one interrupts the flow of afferent impulsation in its receptor zone at the region of the aortic bifurcation [6]. In addition, as was shown by our experiments, this interruption of the impulsation, leading to lowering of the functional level exclusively in the region of the nerve elements comprising the inspiratory center, is accompanied by the disappearance in this region of the original background bioelectric activity [1, 2, 3].

Thus, one must also regard with interest the cause of constant excitation of the receptors in the region of the aortic bifurcation, which leads to the creation of the original background excitation in the inspiratory center. As our investigations showed, the latter is a determining factor in forming the automatism of the frog respiratory center. The works of N. A. Popov and L. B. Vagner [10], and V. M. Karasik [4], noted the important significance of chemical stimuli, which, when their blood concentration was increased, caused dyspnea in the frog.

In this work we describe the results of recording changes in the pulmonary respiration of frogs, and alterations in the physiological parameters within the region of the neural elements comprising their inspiratory and expiratory centers, and in the motor area, as associated with changes in the pressure of the perfusion fluid through the vascular system, the integrity of the aortic receptor zone being preserved.

METHOD

In frogs (Rana esculenta et ridibunda), at the lower end of the aortic bulb, we carefully inserted a canula with a wide and short front, trying not to damage the receptor region. The canula was connected to a Mariott vessel, filled with Ringer's solution. Then the heart was removed, and the fluid washing the vascular system of the frog was withdrawn through a vein. Pulmonary respiration was maintained unchanged as compared with the norm, with a fluid pressure in the range of 27—40 cm of water. Respiration was recorded myographically (we counted the respiratory movements of the muscles at the bottom of the oral cavity). The method of locally measuring the physiological parameters in the regions of the neural elements comprising the respiratory center was described in detail in a previous work [2]. The site of the tip of the focally stimulating microelectrode (30μ) was additionally verified histologically after the experiment.

RESULTS AND DISCUSSION

It should be noted that the reaction of the frog's pulmonary respiration to changes in the vascular pressure could only take place when the receptors of the aortic zone were intact and in good condition. Otherwise, respiration ceased and no changes in the vascular pressure of any kind were reflected in the respiration.

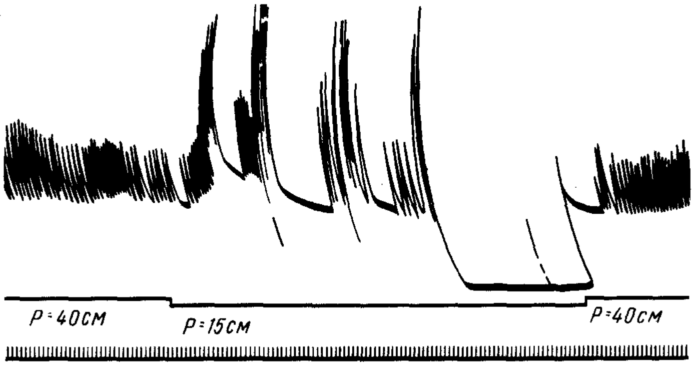

Fig. 1. Myogram of the respiratory movements of the muscles at the bottom of the oral cavity in the frog, during normal pressure of the fluid in the vessels and after its lowering. Upper tracing—respiratory movements; middle—marks indicating changes in the pressure of the perfusion fluid within the vessels; lower—time markings (2 sec). Original pressure—40 cm H_2O. Pressure lowered to 15 cm H_2O.

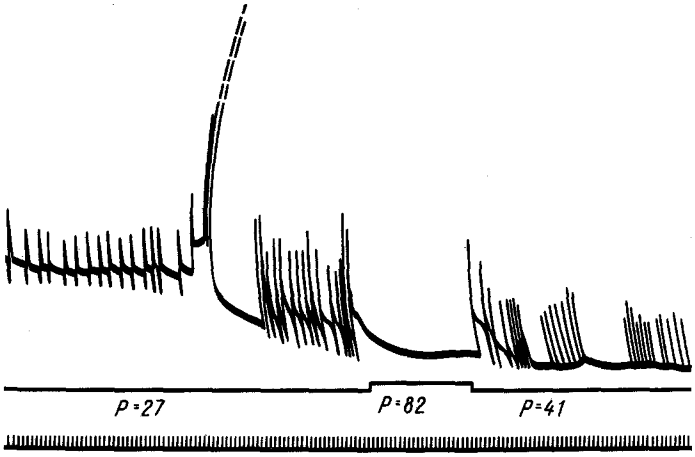

Fig. 2. Myogram of the respiratory movements of the muscles at the bottom of the oral cavity in the frog, during normal pressure and after raising it above normal. Original pressure of 27 cm H_2O. Elevated to 82 cm H_2O. Designations are the same as in Fig. 1.

To illustrate the nature of the change in pulmonary respiration upon lowering the pressure in the vessels, we show the protocol of experiment No. 12, done on February 9th, 1959 (Fig. 1). It can be seen that when the fluid pressure was 40 cm H_2O, the pulmonary respiration was expressed clearly. Upon lowering the vascular pressure to 15 cm (i.e., to less than half), changes appeared within 4 seconds, which first (in the course of 2 minutes) were manifested by a periodic shift from increasingly long pauses in the respiration (pulmonary and oscillatory) to groups of inspirations of increasing amplitude. After this, there ensued complete and prolonged cessation, with a sharp lowering of the tonus of the "inspiratory" muscles; the cessation lasted 68 seconds, i.e., throughout the period that the pressure in the vessels was kept below the original (normal) level. Subsequently, within 4 seconds the tonus of the "inspiratory" muscles was restored, and after 10 seconds normal respiration appeared. In the experiment described the pressure was lowered for 190 seconds. If it was left this way for longer periods of time, the respiration most frequently was markedly disrupted or completely failed to restore itself. Analogous phenomena in the disruption of respiration were observed with blood letting in higher vertebrates, performed by I. R. Petrov (cited by M. V. Sergievskii) [11].

Thus, lowering the blood pressure leads to respiratory arrest. If, after respiration in the frog is restored due to the pressure in the vessels having attained the original (normal) level, the pressure is elevated above the normal level, then one again observes respiratory arrest (Fig. 2). This is well illustrated in the myogram of the experiment performed on December 22nd, 1958. In this case, the fluid pressure at which respiration was observed was equal to 27 cm H_2O. Its elevation to 82 cm immediately caused cessation of respiration and in this case, the amplitude became very small, almost unnoticeable. The difference here was that the cessation of respiration under these conditions was not accompanied by a drop in the tonus of the respiratory muscles, as was observed when the pressure was lowered. Lowering the pressure in the vessels against this setting led to restoration of respiration.

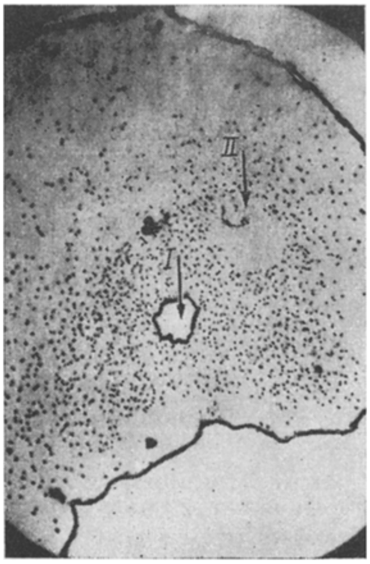

Fig. 3. Histological section of the medulla oblongata of a frog at the level of entrance of the IX and X pairs of cranial nerves. I—mark at the site of the tip of the stimulating microelectrode; II—sensory bundle <u>fasciculus solidarius</u>. Microphotograph made with the use of 9×6 photographic headpiece. Ocul. sim. 15×, obj. plane of chr. 9×0.20. Stained with hematoxylin.

Moissejeff [15] observed the same phenomena of respiratory depression in warm-blooded animals when the pressure in the aorta was increased, and noted its restoration when the pressure was lowered, but he came to the erroneous conclusion that lowering the pressure in general leads to restoration of respiration.

Thus, lowering the vascular pressure below normal, which necessarily decreases the intensity of stimulation to the respiratory centers, and intensifying the vascular pressure, which necessarily leads to an increase in the intensity of stimulation to the centers, both result in the very same phenomenon: respiratory arrest, although the transition to this state in the two cases occurs in different ways.

In connection with these phenomena, it was of interest to elucidate the actual nature of the changes in the functional indices of the neural elements comprising the different regions of the respiratory center, particularly the inspiratory, expiratory, and motor areas. The changes in the physiological parameters which we measured can be illustrated in the following experiments. Thus, for example, in the experiment on November 25th, 1960, when the pressure of the perfusion fluid was 40 cm H_2O and the pulmonary respiration was clearly expressed, the rheobase in the region of the neural elements comprising the inspiratory center was 15 v, the accomodation constant λ was 100 microcuries, and the chronaxie was 0.14 microcuries.

When the fluid pressure in the vessels was lowered to 30 cm H_2O, the rheobase rose to 26 v, i.e., increased by 1.6 times, the accomodation constant now became 72.2 microcuries, i.e., decreased by 1.3 times, and the chronaxie equaled 0.2 microcuries, prolonged by 1.4 times (measurement performed in the course of the first 3 minutes). In this case, respiration of the frog ceased completely. However, with restoration of the original level of pressure in the vessels (to 40 cm H_2O), all the parameters attained their starting values within 20 minutes.

Thus, when the pressure in the vessels was decreased, excitation diminished in the neural elements of the inspiratory center at the same time, and the rate of the accomodation process increased (in this experiment, as was shown by histological verification, the end of the stimulating microelectrode was situated in the area of the neural elements comprising the inspiratory center) (Fig. 3). The described tendencies in the changes of the physiological parameters for the indicated area of the neural elements comprising the respiratory center of the frog, seen with lowering of the perfusion fluid pressure, were also observed in the remaining 20 experiments (Table 1).

TABLE 1. Mean Data of the 20 Experiments Measuring the Physiological Parameters in the Region of Neural Elements Comprising the Inspiratory Center of the Frog Under Normal Conditions and with Lowering of the Pressure in the Vessels

Pressure of 40 cm			Pressure of 30 cm			Pressure of 40 cm		
rheobase (in v)	chronaxie	constant λ	rheobase (in v)	chronaxie	constant λ	rheobase (in v)	chronaxie	constant λ
	in microcuries			in microcuries			in.microcuries	
15,4	0,153	91,3	26,4	0,298	83,28	17	0,123	93,3

TABLE 2. Mean Data of the 20 Experiments Measuring the Physiological Parameters in the Region of Neural Elements Comprising the Inspiratory Center Under Normal Conditions and with Elevation of the Pressure in the Vessels

Pressure of 40 cm			Pressure of 50 cm			Pressure of 40 cm		
rheobase (in v)	chronaxie	constant λ	rheobase (in v)	chronaxie	constant λ	rheobase (in v)	chronaxie	constant λ
	in microcuries			in microcuries			in microcuries	
17	0,123	93,5	29,1	0,162	39,4	17,8	0,119	91,7

The experiments also showed that elevation in the vascular pressure causes changes in the physiological parameters of the region of neural elements comprising the inspiratory center which are analogous to those described above with lowering of the pressure. Thus, for example, in the experiment with restoration of respiration and its parameters, elevation of the pressure to 50 cm H_2O led to a rise in the rheobase from 16 to 29 v, i.e., by 1.6 times. The chronaxie increased from 0.14 microcuries to 0.37 microcuries, i.e., by 2.6 times. The accomodation constant λ decreased from 100 microcuries to 80.5 microcuries, i.e., was lowered by 1.2 times. When the pressure was lowered to the normal level respiration was restored and the parameters were returned to their starting levels. All the other experiments showed the same tendency (Table 2).

Investigation of the physiological parameters in the neural elements of the expiratory center and the motor area under the described conditions of changes in the vascular pressure showed the complete absence of change, or very insignificant alterations within the range of normal fluctuation for readings of the functional level.

Thus, marked changes in the parameters are observed in these experiments only in the regions of neural elements comprising the inspiratory center. They show the same tendency, despite the reverse character of the stimulus: in one case (with lowering of pressure) the degree of stimulation decreases, while in the other (with increasing of the pressure) it increases. It was shown that in both cases excitation decreased, the chronaxie was prolonged, and the process of accomodation was accelerated, and there occurred respiratory arrest and the cessation of automatism. All the above leads to concluding, in the first place, that the initial reaction of the respiratory center to changes in pressure within the vessels is accomplished, primarily, via the influence of the receptors in the aortic zone on the inspiratory center, and is not a result of a direct reaction of the centers to changes in the vascular pressure, nor is it accomplished through the influence of other receptor zones. In the opposite case, the expiratory centers would also react, as we observed when the receptors of the lungs were cut off [3], as well as the neural elements of the motor area. In the second place, the leading role in depression of the respiratory center, in the first moments, both from lowering the vascular pressure as well as raising it, is apparently played by the pressure change itself, and not by an increase in carbon dioxide. This conclusion is supported by the frog's well known ability to maintain normal activity of the nervous system for a long time during interruption of pulmonary respiration [12]. Thirdly, as a result of the enumerated characteristics in the organization of the frog's repiratory center automatism, a leading role is apparently played by the background excitation of the inspiratory center, formed by the constant impulsation from the receptors of the aortic zone, which are constantly excited by a certain degree of pressure in the vessels, and never undergo adaptation. However, in higher animals the activity of the respiratory center is not determined only by activation of one of the receptor zones, but rather a large number of them, since cessation of the background rhythmic impulsation of the inspiratory neurons occurs only with massive deafferentation [6, 16, 17]. In addition, this center possibly acquired the direct receptor function of perceiving the pH of the environment, which is suggested by certain experiments with direct chemical action on the inspiratory region [13]. However, under certain conditions, the old mechanisms can apparently manifest themselves, involving the earlier formed automatic activity of the center [8, 9]. In particular, in association with the phenomena of revival of the organism, a number of authors established that restoration of respiration is the primary determining factor, from which the entire process of revival begins, since restoration of repiration is necessary here not only for oxygen supply, but also because the production of a focus of excitation in the medulla oblongata is necessary for reactivation of the cortex [7]. It should be noted that specifically aortic injection of nutrient fluid under a given pressure is a better therapeutic means than arterial injection for restoring the respiration of an organism being revived, as has been observed by a number of authors [7, 5, 14].

SUMMARY

Both with reduction and with the rise of pressure in the frog's vessels the authors observed in the nervous elements of the inspiratory center an increase of the rheobase, prolongation of chronaxie, and reduction of accomodation constant, accompanied by respiratory arrest. This process was absent in the nervous elements of expiratory and motor areas. A conclusion was drawn that constant afferent impulsation from the baroceptors of aortic zone, creating background excitation in the inspiratory area, plays the leading role in the organization of automatism in the frog's respiratory center. The mechanism may become decisive in organizing the respiratory center automatism in the higher animals in special conditions, for instance in phenomena of body revival.

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