PARTICIPATION OF MEDULLARY RETICULAR NEURONS IN ORGANIZATION OF THE RESPIRATORY ACT

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There have been many investigations of reticular neurons (RN), but the role of these cells in organization of the respiratory act has been inadequately studied. This omission is particularly unfortunate, because the respiratory center (RC) lies in the medullary reticular formation. It has been suggested [5, 8, 9, 12, 18] that the number of RN may be further increased during forced or obstructed breathing. The possibility of a direct role of RN in the transmission of afferent signals to respiratory neurons (RespN) likewise cannot be ruled out. However, these hypotheses have not been confirmed experimentally. The question whether RN are permanently numbered among the RespN or whether their connection with activity of RespN is only temporary in character likewise remains unsolved.

This paper gives the briefly summarized results of an experimental study of this problem, which has been in progress for more than 10 years.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with pentobarbital (45 mg/kg) by the method described previously [3, 4, 11]. In all experiments parallel recordings were made of respiratory movements of the chest and electrical activity of RN and RespN in the medulla. Activity of more than 800 RN was analyzed. The results are divided into four thematic groups.

EXPERIMENTAL RESULTS

1. *Responses of External Respiration, RespN, and RN to Threshold and Above-Threshold Electrical Stimulation of the Central End of the Divided Superior Laryngeal, Vagus, and Sciatic Nerves.* The first points which had to be made clear were whether all medullary RN respond to reflex stimulation, whether a parallel exists between responses of RespN and RN, and what are the latent periods of responses of RespN and RN. It has been shown [8] that by no means all RN respond to stimulation of the nerves mentioned above [2, 13], and that responses of RespN and RN to stimulation are not always parallel (they were parallel in about one-third of cases).

The latent periods of reflex responses of medullary neurons, according to data in the literature [1], vary from 4 to 12 msec. According to our own data [2, 13], during stimulation of the central ends of the superior laryngeal, vagus, and sciatic nerves latent periods of RN vary from 2.4 to 3.2 msec, whereas those of RespN, in the same nucleus ambiguus, vary from 4.1 to 6 msec. However, according to some workers [16, 17], some RespN in the nucleus of the tractus solitarius have monosynaptic connections with sinus and vagus nerves. These data were partly confirmed by V. E. Yakunin: of 16 inspiratory neurons in the nucleus of the tractus solitarius the latent periods to stimulation of the vagus and superior laryngeal nerves varied from 2.5 to 3 msec in four cases, and in the remaining 12, just as in the case of RespN in the nucleus ambiguus, they were 4.1-5 msec. RN are particularly sensitive to the action of adrenalin and noradrenalin [2].

Afferent signals can thus reach RC by two pathways: via RN and via RespN. The first pathway is most widespread, for there are about 100 different synapses on the body of one RN and several thousand synapses on its dendrites [14, 15].

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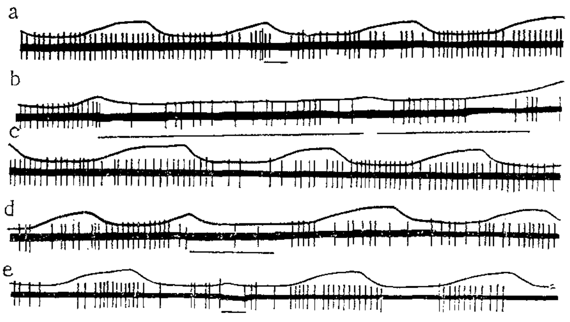

Fig. 1

Fig. 1. Changes in electrical activity of an RN during stimulation of expiratory site of gigantocellular nucleus (from an experiment of V. E. Yakunin). Top trace — respiratory movements; bottom trace — unit activity; short horizontal lines — markers of stimulation.

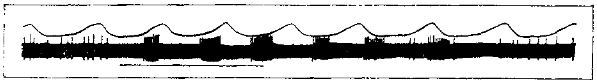

Fig. 2

Fig. 2. Changes in electrical activity of an RN during hypothalamic stimulation (from an experiment of A. V. Naumova). Legend as to Fig. 1.

2. *Responses of RespN and RN in the Medial and Lateral Zones of RC to Electrical Stimulation of Inspiratory and Expiratory Sites, Located in the Gigantocellular Nucleus, Nucleus of the Tractus Solitarius, and Nucleus Ambiguus* [*3, 4, 10*]. These nuclei contain not only RespN, but also RN. It is a noteworthy fact that several dozen reticular neurons are present for every single RespN in the inspiratory and expiratory sites of the gigantocellular nucleus of anesthetized cats, and stimulation of these sites leads to a phase shift in the respiratory cycle, enhancement of electrical activity of RespN functionally equivalent to them, and inhibition of RespN functionally differing from them in both halves of RC and of the spinal cord.

This fact is evidence of the integrative function of these tested sites. A similar functional difference also was found for several other inspiratory and expiratory sites, but it is not present in all of them and varies in degree. Electrical activity of RN also varied: it could be stimulated and inhibited, not always qualitatively equally with responses of RespN observed in a concrete experiment. Functional connections between nuclei are two-way and varied, but preferential connections stand out clearly in this case. Stimulation of inspiratory and expiratory sites of the gigantocellular nucleus predominantly enhances electrical activity of RespN functionally equivalent to the stimulated sites and inhibits electrical activity of functionally different RespN of the nucleus of the tractus solitarius and nucleus ambiguus. Stimulation of the inspiratory and expiratory sites of the latter, however, predominantly inhibits electrical activity of RespN and RN in the gigantocellular nucleus. It was concluded from these results that most RN located in nuclei of the RC are included in its composition, but the functions of these RN are varied: some of them participate in the reception of afferent signals and integration of the respiratory act, others take part in efferent responses.

3. *Responses of RN to Long-Term and Short-Term, but Systematically Repeated Stimulation of Inspiratory and Expiratory Sites of RC and Also of Certain Suprabulbar Lesions of the Brain.* These observations were made in order to study the possibility of transformation of electrical activity of RN into electrical activity of RespN. Theoretically such a possibility can be argued on the grounds that besides inspiratory and expiratory RespN, in the neuronal composition of RC there are also inspiratory-expiratory and expiratory-inspiratory neurons, and continuously discharging neurons with an increase in frequency during inspiration or expiration, which can be regarded as intermediate forms between RN and RespN. During the various modifications of stimulation different responses of RN were observed: intensification, partial and complete cessation of electrical activity, disturbance of the rhythm of activity, and so on. Transformation of electrical activity of RN into electrical activity of RespN was found extremely rarely. One such case is illustrated in Fig. 1, which shows responses of RN during consecutive short-term stimulation of the expiratory site of the gigantocellular nucleus. Transformation of electrical activity of RN into electrical activity of a filled inspiratory neuron can be clearly seen in Fig. 1b. Similar transformation could be obtained by stimulating the hypothalamus during two respiratory cycles. The typical RN became a typical early RespN as regards the character of its activity. After the end of stimulation it discharged like an expiratory neuron and, finally, became an RN once more (Fig. 2).

Similar results also were obtained during stimulation of certain other sites in the brain stem. There is no doubt that with improved techniques of determining functional properties of RN, cases of transformation of their activity into the respiratory type will be multiplied.

4. *Injection of 0.2 ml of Solutions of 5% Cocaine or* 0.1% *Dihydroergotoxin* directly or by microiontophoresis into regions 1-2 mm rostrally to the lower third of the rhomboid fossa, 0-2 mm laterally to the medullary raphe, 4-6 mm from the dorsal surface into the depth of the medial zone and 3 mm rostrally to the obex, 2.5-5 mm laterally to the raphe, and 4-6 mm into the depth of the lateral zone. To visualize the spread of the injected fluids 0.2 ml of Evans' blue was injected and the brain was then examined morphologically [2].

These experiments were carried out to compare changes in respiration and in electrical activity of inspiratory and expiratory RespN. Injection of these blockers into the medial zone, in which almost exclusively RN are active in the anesthetized cat, stops the automaticity of RC after 1-3 respiratory cycles. Respiration can be restored by injecting adrenalin or noradrenalin into the vertebral artery. This effect is reproduced more easily after cocaine than after dihydroergotoxin. After injection of the latter, the effect of adrenalin or noradrenalin is manifested as a rule before respiration has ceased completely. This particular feature of the action of dihydroergotoxin is in all probability associated with the fact that it blocks both membranes of the synapses of adrenoreactive systems almost simultaneously. The same blockers, but injected into the lateral zone, do not stop respiration. Their injection is usually followed by marked disturbances of the dynamics of the respiratory chest movements which vary in degree [2].

This difference in the actions of the same substances suggests on good grounds that if they are injected into the medial zone the inflow of afferent impulses into their principal receptive mechanism, namely definite RN in RC, will cease. If the same substances are injected into the lateral zone, the disturbance of connection of the center with afferent impulses is partial and less marked, and can be compensated by the medial zone.

To sum up the results of the whole series of observations it can be concluded that among the whole complex mass of medullary RN there is a group of RN which undoubtedly belongs to the neuronal apparatus of RC and plays a very important role in its activity. The composition of this group of RN is complex. It includes RN which constitute the basic mechanism responsible for the connection between RC and afferent impulsation. The main mass of these RN lies in the medial zone of the center. The second group of RN is localized in the inspiratory and expiratory integrating sites of the center. These RN, like the RespN also located here, integrate the received signals and take part in the activity of complex effector regions of the respiratory system. The third group of RN lies mainly in the lateral zone of the center. RN of this group are labile in their functions. They can change the character of their electrical activity under the influence of incoming impulses. In particular, by discharging the expiratory site of the gigantocellular nucleus, the pons, or the hypothalamus, the electrical activity of these RN can be transformed into electrical activity of typical RespN.

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CHOLINERGIC AND GABA-ERGIC MECHANISMS CONTROLLING MENTAL RESPONSES IN RATS IN THE EARLY POSTNATAL PERIOD

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In the early postnatal period rats show significantly more motor responses (MR) of the twitch type during sleep than adult animals. Previous investigations showed correlation between the onset of MR of the twitch type and periodic formation of a state of hypoxemia [5].

It is interesting to study the pattern of neurohumoral regulation of MR of the twitch type in rats in the early postnatal period. Significantly higher acetylcholinesterase activity is found in the blood and various parts of the brain of animals at an early age than in adults [6], and this is associated with a low level of inhibitory cholinergic processes in the CNS [1, 2, 8], and also evidently of GABA-ergic mechanisms.

The object of this investigation was to study the role of the above-mentioned mediator systems as factors involved in the neurohumoral regulation of MR of twitch type in rats in the early postnatal period.

EXPERIMENTAL METHOD

The frequency of MR of twitch type was analyzed in noninbred albino rats from the 1st through the 30th day of life. In addition the action of drugs on the character of performance of MR of twitch type was investigated in rats aged 12 days. The MR were recorded by means of special transparent plastic cages to the floor of which piezoelectric transducers were fixed on the outer side. MR (actogram) were evaluated on the ÉÉGP4-02 electroencephalograph. The cages were heated by means of an electric lamp to 25°C. At this temperature the rats quickly fell asleep and began to exhibit MR of twitch type. To analyze the mechanisms of regulation of MR, rats in the experiments of series I were given an intraperitoneal injection of the GABA preparation aminalone (50 mg/kg) and the GABA derivative fenibut (5 mg/kg) [7], and also diazepam (0.3 mg/kg). The last of these drugs increases the sensitivity of receptors to GABA but in large doses it delays GABA deactivation [3] and potentiates GABA-ergic inhibition [3, 9]. In the experiments of series II drugs increasing the acetylcholine concentration were injected into the rats: neostigmine (0.6 mg/kg) and galanthamine (0.1 mg/kg). In series III the action of the muscarinic cholinolytic atropine (0.02 mg/kg) was analyzed. These drugs were dissolved in physiological saline and injected intraperitoneally in a volume of 0.1-0.2 ml. The order of the investigation was as follows. First the initial frequency of MR was recorded, this was repeated after injection of physiological saline, and again af-

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