RESPONSE OF MEDULLARY RESPIRATORY NEURONES TO STIMULATION OF THE VAGUS

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Stimulation of the afferent vagus nerve modifies respiratory movements, the results of which are dependent on the stimulus frequency used. Tonic inspiratory response, inspiratory shift of the respiratory mid-position and an acceleration of respiratory rate were obtained by low-frequency stimulation. High-frequency stimulation, on the contrary, caused prolonged expiration, expiratory shift of respiratory mid-position and slowing of respiration. The apneusis is also affected by afferent vagal stimulation. Low-frequency stimulation prolonged apneusis while high-frequency gave rise to a sustained rhythmic respiration. It must be pointed out here that the words "expiratory" and "inspiratory" used in these literatures, however, stem only from a mere observation of the recorded respiratory curves.

During brain-stem stimulation, it has been found recently by these authors that either simultaneous facilitation or inhibition of the medullary inspiratory and expiratory discharge can be a cause of respiratory acceleration (unpublished observation). In other words, an acceleration of respiratory rate is not always resulted from increased activity of respiratory center, but also brought about by inhibition of respiratory discharges of medulla. From this finding arises the question; 1) if inspiratory and expiratory responses to vagal stimulation are actually resulted from increased activity of inspiratory or expiratory neurones respectively and 2) whether respiratory acceleration, which is observed during low-frequency stimulation, is derived from facilitation or inhibition of the medullary respiratory discharges.

In this paper, therefore, an attempt was made to see the changes of respiratory discharge of the medulla during vagal stimulation at low- and high-frequencies.

METHODS

Rabbits were anesthetized with urethane in a dose of 1.2 g per Kg body weight. After tracheotomized, both carotid arteries were ligatured and the vagi were roughly

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147
stripped off from the surrounding connective tissues in a length of a few centimeter and were cut at the level of just before entering thorax. Two small incisions were made on the skin of the dorsal neck and the central stems of the vagi were sticked out of the holes, passing through the neck muscles. In case of stimulation, the cut end of the vagus was lifted up and placed on the stimulus electrode. This procedure was found to be more reliable than the use of embedded electrodes. A part of the occipital bone and the dura were removed, but the cerebellum was left intact. A small pool thus made on the fourth ventricle was filled by liquid paraffin. Steel electrodes, the exposed tip diameter of which was less than a few micra, were used for the recording of respiratory discharges. Nerve impulses were picked up by a cathode follower, amplified with a time constant of 3 msec and displayed on one beam of a dual beam oscilloscope, as well as on an audiomonitor.

For the recording of respiratory movements, a metal plate was placed on the back of the animal. The capacity change between the stereotaxic frame and the metal plate was registered by an electronic manometer and recorded on the second beam of the oscilloscope. The intensity of the second beam was so arranged to be modulated by the pulse of stimuli. The stimulus was an isolated rectangular pulse, 1 msec in duration, 2 or 5 volts in intensity and 30 or 300 cycle per second in frequency. The rectal temperature of the animal was checked regularly and kept in a physiological range by an intermittent radiation of infra-red lamp.

RESULTS

Periodic bursts of impulses in phase with respiratory movements were recorded from the bulbar reticular formation. Although systematic exploration of the medulla oblongata was not made in this study, respiratory discharges were found in those areas described by several investigators\(^1,4,10\). Expiratory neurones were less frequently encountered than inspiratory neurones and these two neurones were found to be intermingled. Indeed, it happened that inspiratory and expiratory discharges were picked up simultaneously by one electrode. A finding that low-frequency stimulation of the vagus induces a weak inspiratory response and high-frequency stimulation results in a strong expiratory response was generally reconfirmed. In some rabbits, however, both low- and high-frequency stimulation caused inspiratory response. The reason for this is not clear. The decreased excitability of the vagi may be responsible, because it is known that the expiratory effect is abolished sooner than the inspiratory effect when the vagi are blocked by urethane-Ringer solution\(^10\).

In addition to inspiratory and expiratory effect, acceleration of respiration accompanied by decreased amplitude was observed occasionally during low-frequency stimulation. The respiratory mid-position thereby shifted more or less to the inspiratory side.

**Inspiratory Response.** Fig. 1 shows the inspiratory discharge during vagal stimulation at the frequency of 30 c.p.s. This discharge was continuous but increased their frequency in inspiratory phase. Upon stimulation,
FIG. 1. Inspiratory discharge of the medulla during vagal stimulation at a frequency of 30 c.p.s. The intensity of the beam for respiratory movement was modulated by stimulus pulse. Stimulation is indicated as a dotted or heavy dark line in this and following figures.

FIG. 2. Expiratory discharge of the medulla during vagal stimulation at a frequency of 30 c.p.s. Continuous record.

its inspiratory bursts lasted for a considerable time and sustained inspiration ensued. The discharge rate, however, did not increase or decrease compared with that of control inspiratory phase. The only difference between the two is the duration of burst. Changes of the expiratory discharges in response to the same stimulus are illustrated in Fig. 2. During stimulation, the expiratory discharges were not abolished but their intervals were remarkably prolonged. The discharge lost their periodic appearance and gave way to an irregular train of impulses of decreased firing rate.

Expiratory Response. Vagal stimulation at the frequency of 300 c.p.s. inhibits the inspiratory movements. Inspiratory discharges were suddenly arrested and occurred immediate cessation of inspiratory act (Fig. 3). On prolonged stimulation, however, inspiration broke through. On the other hand, expiratory discharges made their appearance upon stimulation even if the stimulus was given just after the expiratory phase and lasted for a con-
siderable time at a constant firing rate (Fig. 4). Like inspiratory discharges in inspiratory response, the expiratory discharges prolonged the duration of bursts, but did not change their discharge frequency during expiratory response.

*Acceleration of respiration.* In this type of response, inspiratory shift of the mid-position was often accompanied as shown in Fig. 5A. Both inspiratory and expiratory discharges were seen periodically during stimulation. Bursts of impulses occurred more frequently, but the rate of firing in each burst was reduced evidently in both inspiratory and expiratory neurones.
DISCUSSION

According to Dirken and Woldring\textsuperscript{3), “the normal inspiratory volleys in the medulla oblongata are modified by a 9/sec. vagal stimulation to a continuous discharge of low frequency; on high-frequency stimulation they disappear completely. The expiratory neurones react with a continuous discharge both on low- and on high-frequency vagal stimulation.” Based on these results, they concluded that both low- and high-frequency stimulation inhibit the inspiratory center. This conclusion is hardly accepted because, as shown in our record of inspiratory responses to low-frequency vagal stimulation, the inspiratory neurones fire at the same rate as in control inspiratory phase. Our results, in addition, indicate the inhibition of expiratory activity during inspiratory response.

On the other hand, HukuHara et. al.\textsuperscript{5) observed a transient increase of inspiratory discharge followed by an abolition. In their report, however, stimulus frequency used was not mentioned and the changes of expiratory neurones were not recorded. In our experience, a transient increase of discharge frequency of both inspiratory and expiratory neurones did occur in response to vagal stimulation, but only when the stimulation was followed by gross movements of the neck and trunk. Indeed, a marked increase of respiratory discharge and a gross bodily movement were caused simultaneously by the stimulation of the sciatic nerve. Our unpublished observation revealed that the stimulus given to the brain-stem reticular formation facilitates both inspiratory and expiratory neurones. The increased activity of inspiratory neurones observed by HukuHara et al. is more likely to be due to the non-specific facilitatory influence of the brain-stem which is called into action by vagal stimulation. In fact, the protocol presented by these authors tells us that the respiratory movement thereby evoked is not a typical inspiratory response to low-frequency vagal stimulation but a momentary increase of inspiratory amplitude.

An outline of the results obtained is schematically represented in Fig. 6. From this figure, it is apparent that low-frequency stimulation inhibits expiratory neurones and high-frequency stimulation inhibits inspiratory neurones. Complete abolition of expiratory discharges was not observed in inspiratory response, while inspiratory neurones failed to fire in expiratory response. The vagal inhibitory effect prevails on inspiratory neurones. In short, the effect of the afferent vagal stimulation on respiratory neurones has been proved to be purely inhibitory.

It remains for now a matter of discussion, whether the frequency dependent effect is attributable to the character of the respiratory center or to that of vagal fibers.
Reciprocal relationship between inspiratory and expiratory neurones in a sense postulated by Pitts et al. may be admitted even if one insists on the essential involvement of the pneumotaxic center in a formation of respiratory periodicity. The nature of this relationship, however, has not been so far fully worked out. Recently, evidence is accumulating which indicates that sustained firings of inspiratory or expiratory neurones are brought about by inhibition of their opposite activity. Salmoiraghi and Burns postulated that the respiratory periodicity is due to a mutual inhibition of inspiratory and expiratory self-reexciting neurones. The respiratory mechanism may be regarded as something like bistable trigger circuits. If such an analogy is correct, inhibition of either inspiratory or expiratory neurones should be accompanied by continuous activity of the other. This speculation has been partially supported by us. As is clearly seen in Fig. 6, the inspiratory and expiratory bursts gave way to a continuous train of firing during inhibition of their opposite activity.

**SUMMARY**

1. Effects of afferent vagal stimulation were observed on medullary respiratory discharges of urethanized rabbits.
2. In a weak inspiratory response caused by low-frequency stimulation, in-
spiratory bursts gave way to a continuous firing, the frequency of which, however, remained unchanged compared with that of control inspiratory discharges. The discharge intervals of expiratory neurones were prolonged.

3. In a strong expiratory response caused by high-frequency stimulation, inspiratory discharges were abolished completely. Changes of expiratory discharges were identical with those of inspiratory discharge in inspiratory response mentioned above.

4. In a respiratory acceleration, both inspiratory and expiratory discharges were inhibited; numbers of firing per bursts were decreased remarkably and their discharge intervals were prolonged.

5. Based on these results, the conclusion was drawn that the inspiratory and expiratory responses to low- and high-frequency vagal stimulation were brought about by inhibition of expiratory and inspiratory neurones respectively.

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LITERATURES


