THE SIGNIFICANCE OF AFFERENT VAGAL INFORMATION IN THE CONTROL OF BREATHING IN GUINEA PIGS

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Abstract. The stimulation of the central vagus nerve in guinea pigs was applied to study the role of vagal afferent information in the control of breathing. The survival time after bilateral vagotomy was measured in unanesthetized animals, under Hexobarbital anesthesia, and in anesthetized subjects when the central stump of the vagus nerve was stimulated. There were no differences in survival time between the first and the second groups, but in animals with vagal stimulation, the survival time was prolonged. The respiratory and circulatory disturbances were abolished by stimulation.

INTRODUCTION

Data dealing with the effects of vagotomy in the guinea pig show that vagus nerves play an important role in the mechanism of the central control of breathing. This is mainly based on the observation that these animals died within a few hours after bilateral vagotomy. Numerous studies on different aspects of this problem have not answered the question concerning how the vagus nerves cooperate with the brain stem “controller” of respiration, nor have they elucidated the mechanism of death following bilateral vagotomy. The well known result of the bilateral vagotomy is the decrease in the rate of respiration, which has a very dramatic course in guinea pigs. It has been found that within a few minutes after cutting both vagi, frequency of breathing decreases to a few breaths per minute (8).
Changes in the pattern of breathing due to vagotomy have been also extensively discussed in the literature. According to Manni and Cassiano (7), vagotomy and midcollicular decerebration cause an apneustic type of breathing. This result was criticised by Wyss (14); according to him it is difficult to show a sustained inspiratory tonus having pneumographic records as the main experimental method. However, Desole and Sotgiu (2) have supported the finding of Manni and Cassiano by recording the electrical activity of intercostal muscles. Since the vagotomy in unanesthetized guinea pigs induces lung edema, attempts were made to examine the mechanism of this phenomenon (10, 12). In the present paper, we re-investigated the problem to ascertain why the vagus nerves are so important for sustained respiratory rhythmicity in guinea pigs.

METHODS

The experiments were performed with 30 adult guinea pigs weighing from 250 to 500 g assigned to one of three conditions:

1. Six guinea pigs were surgically prepared under ether anesthesia. A glass cannula was inserted into the lower cervical trachea, and both vagus nerves were separated from the surrounding tissue and severed when the animal recovered from anesthesia. Survival time was measured for this group.

2. In a second group of 11 guinea pigs hexobarbital anesthesia was induced in doses of 50 mg/kg injected intraperitoneally and supplemental doses were added when needed. The animals were tracheotomized, and the left carotid artery was cannulated to measure the blood pressure with a mercury manometer. An electromyogram of the diaphragm (EMG) was recorded with a bipolar needle electrode. Action potentials were amplified and photographed from a dual beam oscilloscope (Cossor 1035 AK II) on the second channel of which ECG was recorded.

3. Thirteen guinea pigs were also anesthetized with hexobarbital, and all the preparations were the same as in the second group. After the bilateral vagotomy, the central end of the cut vagus nerve was stimulated by the activity of the single pulmonary stretch receptor recorded earlier on magnetic tape or with rhythmic volleys of impulses delivered by a programmed pulse-generator. Electrical stimulation was also used by Oberholzer and Steiner (9) in their investigation of vagus nerves in guinea pigs. Further, the effectiveness of this method for certain purposes was also demonstrated by Karczewski (5). A threshold voltage was adjusted (0.5–3 v) for the tape stimulation, and optimal frequency of impulses (50–100 imp/sec) and time duration of volleys (0.3–0.5 msec) were chosen for the pulse generator. The central end of the severed vagus
nerve was placed on bipolar platinum electrodes and covered with paraffine. In the third group, the survival time, as well as the dependent variables measured for the second group, were indexed. In some cases, the animals were artificially ventilated and their vagus nerve was not stimulated. Additionally, for several subjects, blood oxygen saturation was estimated with Oxymeter 057 (USSR origin) and $pCO_2$ was measured in blood samples (Astrup, Radiometer).

RESULTS

**Group 1.** The survival time after bilateral cervical vagotomy in unanesthetized guinea pigs was $2.86 \pm 1.02$ hr (mean $\pm$ SE). The survival time for Group I is indicated in Fig. 1B; the vagotomy was followed by a progressive decrease in the frequency of breathing. Edematous froth in the tracheal tube appeared about 0.5 hr after vagotomy, suggesting that death might be due to the lung edema which developed after vagotomy. However, the results of the remaining groups indicated that the problem may be more complex, since anesthetized animals survived for a period comparable to the unanesthetized subjects, but without lung edema.

**Group 2.** For this group the survival time was $2.23 \pm 1.41$ hr on average (Fig. 1A). Five minutes after cutting both vagi, the frequency...
of breathing decreased to approximately 60% (Fig. 2B). As the data indicate, the decreased breathing was mainly due to prolongation of inspiration, a typical effect of vagotomy. Fifteen minutes after vagotomy a further decrease in the frequency of breathing was observed. At that time the eupneic pattern of breathing changed to gasp (Fig. 2CDF). These changes were accompanied by systemic hypotension and bradycardia. The sequence of events was as follows: During long-lasting expiratory pauses, bradycardia and hypotension developed progressively. At the top of these changes a gasp appeared after which the heart rate and blood pressure tended to regain control levels (Fig. 3FG). These respiratory and circulatory changes were observed until respiration ceased. The control level of blood oxygenation was 92–98%, and after 1 hr of gasping-like breathing the blood oxygen saturation was 57–70%. Similarly, the control level of pCO₂ was 35 mm Hg, and during long expiratory pause rose to 96 mm Hg. Considering the disturbances in blood gas exchange, one should conclude that the observed pattern of ventilation was inefficient.
Fig. 3. Traces as in Fig. 2. A, vagi intact; B, 1 min after cutting both vagi; C, during stimulation of the central stump of one vagus nerve by pulmonary stretch receptor activity; from D to G, a fragment of one respiratory cycle while stimulation has been stopped; H, artificial ventilation. Note that circulatory changes are absent both during stimulation and artificial ventilation.

**Group 3.** This treatment was included to ascertain if it is possible to prolong the survival time of the vagotomized guinea pig by stimulation of the vagus nerves. The result suggested a positive finding, since subjects were kept alive for an average of $9.25 \pm 5.97$ hr (Fig. 1C). In one case, a guinea pig survived 25 hr, and died only when stimulation was stopped. The scatter of the results can be explained by deterioration in the efficiency of stimulation which may have been due for example, to impaired nerve-electrode contact. In other subjects, it was possible to influence the respiratory rhythm so effectively that the effect of vagotomy was abolished (Fig. 4). During stimulation the circulatory changes did not appear (Fig. 3C). When stimulation was terminated, the changes typical of the second group immediately appeared (Fig. 3D–G). However, when the animal artificially ventilated, the circulatory disturbances disappeared again, which is indicated in bottom trace of Fig. 3.
DISCUSSION

Our results support the view of Oberholzer and Schlegel (8) that proper activity of the respiratory neurons of the guinea pig depends upon vagal information. It has been shown that artificially restored vagal-central feedback enabled an adequate respiratory rhythm and significantly prolonged the survival time of the experimental animals after vagotomy. At the same time the results of the third group have shown that the ventilatory and circulatory disturbances described in the second group are due to the central respiratory failure and not to lung deterioration. It seems clear that bradycardia and hypotension are secondary to inefficient ventilation since all the maneuvers which improved ventilation had a protective effect upon circulatory failure. Moreover, during a respiratory disfunction, even a single gasp was able to normalize temporarily the heart rate and blood pressure.

It is difficult to interprete the protective effect of the anesthetic drugs against the incidence of lung edema after vagotomy. However, it is well known that the large number of anesthetics counteract the adrenaline-induced lung edema (4). A beneficial effect of chlorpromazine on lung edema has also been shown in patients (6). It is possible that anesthesia has a nonspecific action through a sympathetic system. Lung edema induced by vagotomy in conscious guinea pigs has been studied by Schmidt and Meyers (12) and Rech (10). These results suggest that afferent vagal pathways are largely involved in the mechanism of lung edema. In a discussion of the role of anesthetic drugs in the respiratory response to vagotomy, the use of urethane anesthesia should be considered. Oberholzer and Schlegel (8) have found that guinea pigs survived
longer after vagotomy under urethane anesthesia. They assumed that urethane increases the excitability of the respiratory neurons to CO₂ and concluded that extra-vagal mechanisms seem more effective in their action on the respiratory centers. Controversial results were described by Floréz and Borison (3) who found a depressant effect of some anesthetics, including urethane, on the response to CO₂ in the cat.

In the present experiment, attention has been focused on the mechanisms of death after vagotomy. In the interpretation of the first group's results, it is reasonable to assume that lung edema and asphyxia were the direct cause of death. However, different interpretation could be proposed for the results with the anesthetized subjects, since data revealed major changes in the pattern of breathing. Soon after bilateral vagotomy, a progressive decrease in respiratory rate was observed, and after 30 min eupneic breathing was substituted by gasps. This type of breathing could be compared with the findings described by Tang (13) in "medullary" cats. The gasping rate was reduced when air was changed to oxygen, while 7% CO₂ did not alter the gasping. The present data allow to assume that gasping is elicited by hypoxia. Conversely, eupneic breathing was restored by vagal stimulation or artificial ventilation. Relating our results to those described by Tang, it seems that the vagus nerves in the guinea pig play a function of pontine centers in relation to the medulla, which does not necessarily imply that a pneumotaxic center does not exist at all in guinea pigs. Manni and Cassiano (7) have localized the pneumotaxic center in the guinea pig within the anterior part of the tegmentum. However, this is not fully documented since their conclusion is based on the apneustic type of breathing, which appeared after a vagotomy combined with decerebration at midcollicular level. As previously mentioned their conclusion has been criticized by Wyss (14). Also the present results contradict those of Manni and Cassiano (7), since guinea pigs without central lesions responded to the bilateral vagotomy with a severe respiratory failure, which was exhibited by a dramatic drop in the respiratory rate with standstill of breathing in expiration, which is an opposite feature to the prolonged inspiratory spasm. Desole and Sotgiu (2) have repeated the experiment of Manni and Cassiano (7) and partly confirmed their findings by recording a single apneustic spasm, followed by a short period or rhythmical breathing, and death preceded by gasps. It is worth emphasizing that decerebration did not influence the respiratory rate when the vagus nerves were intact. In view of previous data, the central structures with which the vagus nerves cooperate in sustaining rhythmical breathing remain obscure. It may be concluded that the central organization of breathing in the guinea pig is different from that of other mammals. Afferent information from the lungs de-
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terminates the activity of the central structures responsible for eupneic pattern of breathing in the guinea pig. In this situation the self-limitation mechanism of the medulla, described by Burns and Salmoiraghi (1, 11), could be excluded.

**Conclusions**

1. Vagal activity exerts an excitatory influence on the central structures responsible for rhythmic breathing.
2. Bradycardia and hypotension observed after vagotomy seem to be secondary to respiratory failure and hypoxia.
3. There is evidence that the central organization of breathing in the guinea pig is probably different from other species.

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**REFERENCES**


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