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RESPONSES OF RESPIRATORY NEURONS OF THE RABBIT TO SOME EXCITATORY AND INHIBITORY STIMULI

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Abstract. The effects of an afferent stimulation of the vagus nerve, hypercapnia and hyperventilation on the discharges of pontine, medullary and phrenic respiratory neurons were studied. The responses were investigated in spontaneously breathing, lightly anaesthetized rabbits with intact vagi, and subsequently during artificial ventilation, after vagotomy and under surgical anaesthesia. We found that the patterns of activity of respiratory neurons depend upon the integrity of vagal conduction, pattern of ventilation and depth of anaesthesia, and that vagotomy and deep anaesthesia markedly modify, and sometimes even reverse, the responses of these neurons to respiratory stimuli. The pre-vagotomy type of response can be restored by stimulating the central end of a cut vagus nerve with standard pulses triggered by action potentials recorded simultaneously from the animal respiratory unit. The significance of these findings is discussed.

The activity of the ponto-bulbar respiratory complex depends on many neural and chemical factors whose relative significance and mechanisms of interaction are still poorly understood. Several problems of fundamental importance — e.g. the role of vagal information in the respiratory response to CO_2, or the effects of anaesthesia on the functional organization of the respiratory control system — have not yet been clarified (*see* Guz et al., 1970, Karczewski 1970*a*, 1971).

Many authors (Fernandez de Molina and Wyss 1950, Oberholzer and Schlegel 1957, Karczewski 1965) attempted to explain the role of the vagus nerves in the control of the rate and amplitude of breathing on the basis of experiments in which they were applying an electrical stimulation of the central end of a cut vagus nerve. The mechanisms of respiratory responses elicited in this way remain, however, still controversial.

The stimulation may affect at least two different groups of afferent vagal fibres — pulmonary stretch and irritant (J. G. Widdicombe, personal communication); on the other hand, the functional organization of the "black box" is obviously too complex to allow definite conclusions without taking into account the responses of the individual components of the ponto-bulbar system to a stimulation of only one of its sensory inputs. However, there are only few papers dealing with the effects of an afferent stimulation of the vagi on the medullary (Hukuhara et al. 1956, Nakayama and Hori 1964) or pontine (Bertrand and Hugelin 1971) respiratory neurons.

Well aware of all the drawbacks of the technique of an electrical stimulation of a mixed nerve we decided to re-investigate the role of the vagal input to the respiratory "centres" under various physiological conditions and in response to various stimuli.

Respiratory effects of the afferent stimulation of the vagus nerve

The experiments were performed with male rabbits weighing from 2.5 to 3.5 kg, under light and deep anaesthesia (chloralose-urethan, 1–3 ml per kg of body weight, respectively [1]). The rabbits were breathing spontaneously or paralysed with gallamine (Flaxedil-Specia 20mg or Tricuran-Germed 40mg) and artificially ventilated with a Zimmermann respirator. The discharges of pontine and medullary respiratory units were recorded extracellularly by means of glass microelectrodes filled with agar-KCL solution (Bystrzycka et al. 1970*a*). The activity of C_3 root of the phrenic nerve (or of its single fibre) was recorded in a conventional manner. In some cases the phrenic discharges were integrated and then averaged by means of ANOPS-2 average response computer. End-tidal CO_2 percentage was continuously monitored by a rapid infrared analyser (Godart-Capnograph KK). The records were displayed on an oscilloscope (Tektronix 561 or 565) and filmed. Both vagus nerves were dissected on the neck and cut; one of them was placed on platinum electrodes connected via stimulus-isolation unit with a pulse generator (Tönnies).

The following patterns of stimulation were used (Fig. 1):

1. Continuous, low-and high frequency;

2. Rhythmic, with trains of impulses adjusted to imitate the physiological discharges of pulmonary stretch receptors (Karczewski 1965);

3. Rhythmic, with standard pulses triggered by simultaneously recorded action potentials of a pontine, medullary or phrenic unit ("self-stimulation").

[1] 1 ml of the solution contained 400 mg of urethan and 17 mg of chloralose.

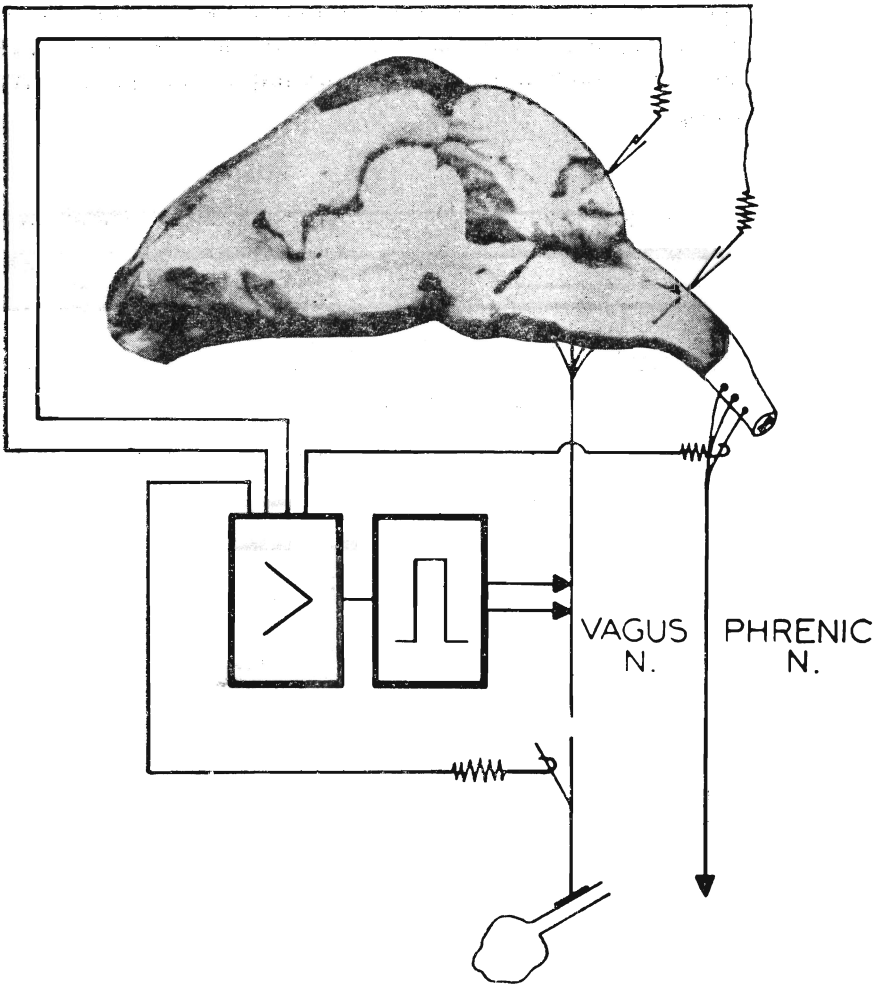

Fig. 1. Schematic explanation of the technique of stimulation of the vagus nerve (*see* text).

In all cases threshold intensity for the respiratory response was used [2].

1. In spontaneously breathing, vagotomized rabbits a continuous, low frequency stimulation (10–40 imp/sec) elicited regularly an inspiratory apnoea and tonic firing in all inspiratory units. However, this effect

[2] Change in the ventilatory pattern in spontaneously breathing or change in the firing pattern of respiratory units in artificially ventilated rabbits; it was assumed that under these conditions only rapidly conducting vagal fibres are stimulated (Fernandez de Molina and Wyss 1950, Oberholzer and Steiner 1956). In the rabbit the threshold intensity oscillates between 16 and 30 μa (Karczewski 1965) which corresponds to 0.8–1.2 v.

could hardly be regarded as a direct excitation of inspiratory neurons, since their firing frequency was always close to the lowest control values. High frequencies (150–1000 imp/sec) were inhibitory to the activity of these neurons (Fig. 2).

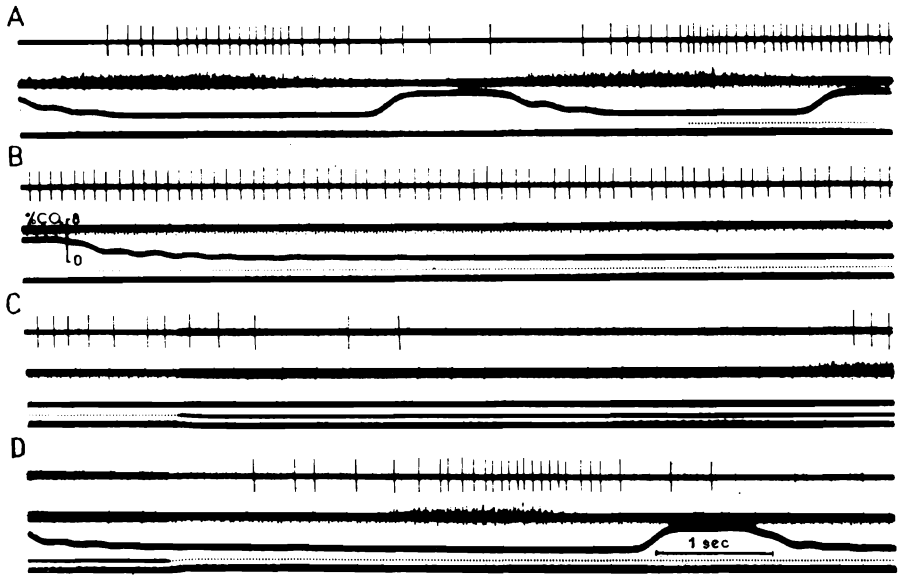

Fig. 2. Effects of stimulation of the vagus nerve on the discharges of a medullary inspiratory neurone, phrenic n. activity and respiratory rate in a spontaneously breathing, vagotomized rabbit. Traces from top to bottom: unit discharge, phrenic n. activity, end-tidal CO_2%, stimulus marker. *A*, control, start of stimulation (40 imp/sec); *B*, continuation of *A*; *C*, after 1 min, stimulation switched to 1000 imp/sec; *D*, after 1 min, stimulation switched again to 40 imp/sec. In this and the other Figures spike potentials retouched.

These responses of pontine and medullary expiratory units presented almost a mirror image of the inspiratory ones; low frequencies (10–40 imp/sec) reduced the discharges and high (150–1000 imp/sec) elicited continuous firing.

In artificially ventilated rabbits the stimulation produced similar effects; Fig. 3 presenting an expiratory unit of the pons shows a typical, continuous firing in response to high frequency (300 imp/sec) stimulation, with concommitant inhibition of phrenic nerve activity. In contrast to spontaneously breathing animals in which low frequency stimulation elicited always an inspiratory apnoea, in paralyzed rabbits frequencies between 10–40 imp/sec regularly accelerated the central respiratory frequency.

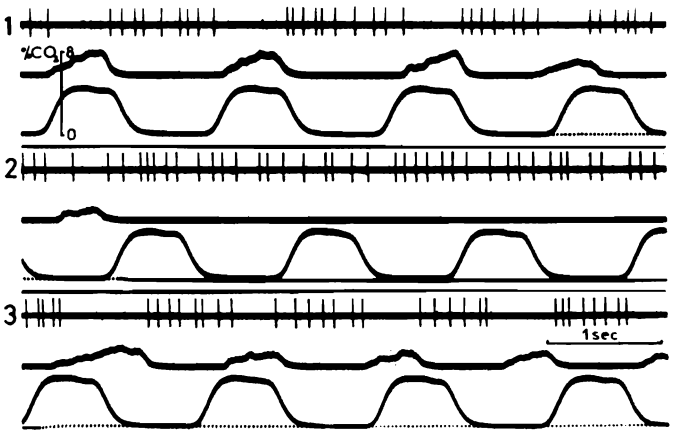

Fig. 3. Effects of stimulation of the vagus nerve on the discharges of pontine expiratory unit and phrenic n. activity in artificially ventilated, vagotomized rabbit. Traces from top to bottom: unit discharge, integrated activity of the left phrenic n. (upwards deflection), end-tidal CO_2, stimulus marker. *1*, control, start of stimulation (30 imp/sec); *2*, after 30 sec stimulation switched to 300 imp/sec; *3*, after 30 sec stimulation switched again to 30 imp/sec.

An addition of the anaesthetic changed the pattern of firing and usually enhanced the expiratory-facilitatory effects of high frequency stimulation, whereas the expiratory-inhibitory response to low frequencies was reduced (Fig. 4). On the other hand, even in cases when a full anaesthetic dose of sodium pentobarbitone (Nembutal Abbott — 30 mg/kg) was given to an animal previously anaesthetized with chloralose-urethan, we were not able to confirm the observation of Hukuhara et al. (1969) who found that anaesthesia, and particularly pentobarbitone, inhibits respiratory discharges in the pons of cats. There is no obvious explanation for this discrepancy except that there might be species differences; our unpublished observations indicate that rabbits are fairly resistant to halothane and high concentrations of this anaesthetic (3–4 vol.%) are necessary to produce surgical anaesthesia.

2. Earlier investigations showed that the whole respiratory system can be driven within fairly wide limits of frequencies by rhythmic trains of electrical pulses applied to the central end of a vagus nerve (Karczewski 1965). Using this technique in the present experiments we found that the respiratory neurons throughout the brain stem respond in a uniform way to the given pattern of stimulation. The phenomenon of resetting the respiratory rhythm in spontaneously breathing rabbits and the central respiratory activities in paralyzed ones was accompanied by marked changes in the pattern of firing of the expiratory neuron pool whereas the inspiratory units seemed to follow the "vagal drive" without signifi-

cant change in their discharge pattern. Figures 5 and 6 present representative experiments; the expiratory-inhibitory effects of low frequency stimulation and expiratory-facilitatory effects of high frequency stimulation can be seen quite clearly.

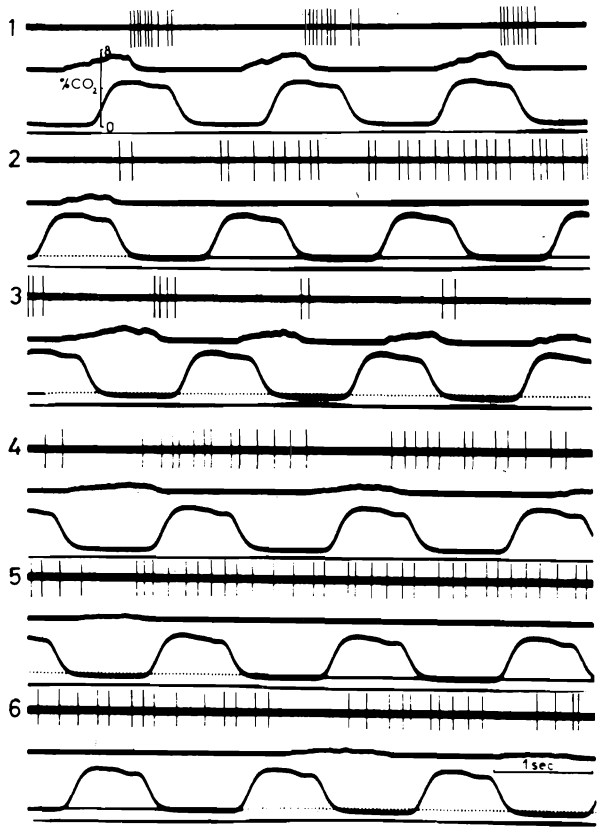

Fig. 4. Effects of anaesthesia on the response of a pontine expiratory unit and phrenic n. activity to stimulation of the vagus nerve in anaesthetized, vagotomized and artificially ventilated rabbit. Traces, like in Fig. 3. *1*, control run; *2*, stimulation (300 imp/sec); *3*, stimulation (30 imp/sec); *4*, control after an i.v. injection of 2 ml of chloralose-urethan mixture; *5*, stimulation 30 imp/sec switched to 300 imp/sec; *6*, stimulation 300 imp/sec switched to 30 imp/sec.

The results obtained in the first two groups of experiments gave some evidence which seems to support the view (*see* Bystrzycka et al. 1970*b*) that the afferent activities of the vagus nerve may primarily modify the activity of the expiratory component of the ponto-bulbar respiratory complex, the inspiratory neurone pool being affected secondarily. An addition of an anaesthetic increased the threshold of the response to sti-

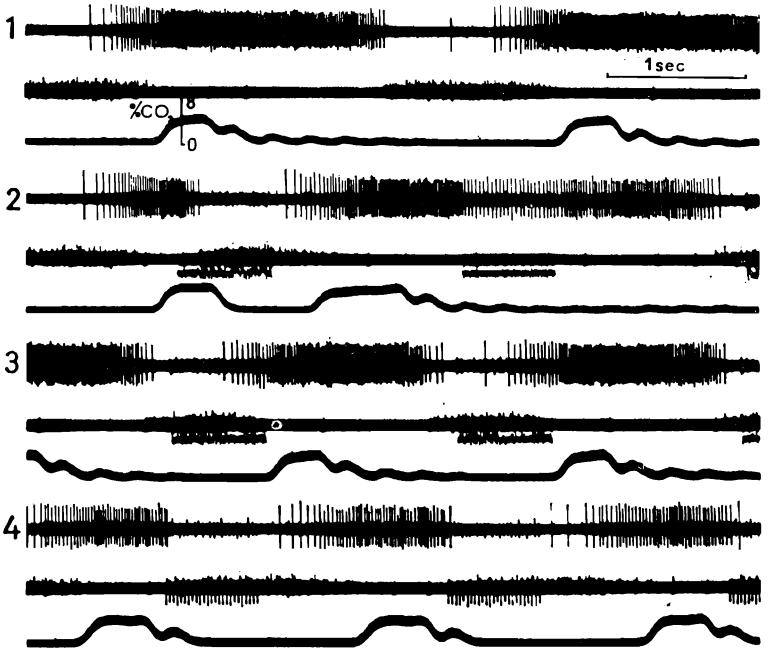

Fig. 5. Effects of rhythmic stimulation of the vagus nerve on the discharges of a medullary expiratory unit, phrenic n. activity and respiratory rate in a spontaneously breathing, vagotomized rabbit. Traces from top to bottom: unit discharge, phrenic n. activity and superimposed stimulus marker (downwards), end-tidal CO_2%. *1*, control run; *2*, start of stimulation (150 imp/sec, duration of a volley 400 msec); *3*, after 1 min; *4*, after 1 min of stimulation, 40 imp/sec. Note the synchronization of volleys with different phases of the respiratory cycle.

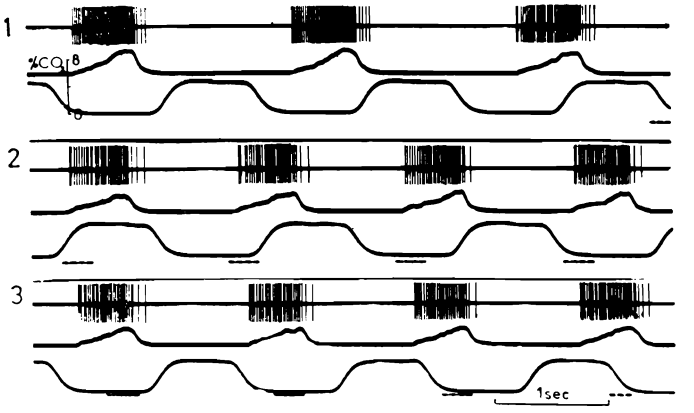

Fig. 6. Effects of stimulation of the vagus nerve on the discharge of a pontine inspiratory unit, and phrenic n. activity in artificially ventilated, vagotomized rabbit. Traces like in Fig. 3. *1*, control run; *2* and *3*, after 1 and 2 min of rhythmic stimulation (100 imp/sec, volley duration 300 msec).

mulation, the expiratory-inhibitory effects of low frequency stimulation being abolished earlier than those of high frequency (i.e. expiratory-facilitatory). Of course, further studies dealing first of all with latencies are necessary.

3. The third group of experiments was intended to answer the question to what extent does the central respiratory rhythmicity depend upon the presence of a rhythmic activity at the vagal sensory input.

The results obtained in this group seem to indicate that the rhythmic activity of the vagi may play an important role as a factor controlling the level of excitability of the ponto-bulbar respiratory complex (apart from the "specific" reflex effects elicited from a given type of pulmonary vagal endings). In each case, when the "self stimulation" was switched on in a vagotomized rabbit there was a smooth acceleration of respiratory rhythm until a steady state (usually close to the pre-vagotomy values) was obtained. The type and magnitude of the response reflected the pattern of activity arriving via the vagus nerve. Also these effects were quantitatively affected by the depth of anaesthesia (Fig. 7).

We concluded that the "self stimulation" technique might be useful for distinguishing between central and peripheral effects of some respiratory stimuli. Since this method of stimulation appeared to abolish the respiratory effects of vagotomy inspite of the fact that the respiratory "centres" remained disconnected from the vagal receptors in the lungs and airways, it seemed justified to use it in cases when the relative importance of reflex vz. central component of a response is not clearly distinguishable. We hoped that the presence of an "artificial vagal feedback loop" could be particularly useful for studying the responses to carbon dioxide. It is well known that vagotomy reduces the frequency response of the respiratory system to hypercapnia (*see* Richardson and Widdicombe 1969, Euler et al. 1970) but it is not clear if it happens because the inflow of excitatory information from the lungs and airways is interrupted, or because vagotomized animals are, in general, more or less unable to increase respiratory rate in response to various stimuli (Glebovskii and Pavlova 1962). Before we decided to study this particular problem, the responses to low and high CO_2 had been investigated under various experimental conditions.

The effects of hypercapnia and hyperventilation on the activity of the respiratory neurons in the rabbit

The animals were studied before and after bilateral vagotomy, under light and surgical anaesthesia, breathing spontaneously or artificially ventilated (*see* above). Pontine or medullary unit discharge, phrenic nerve

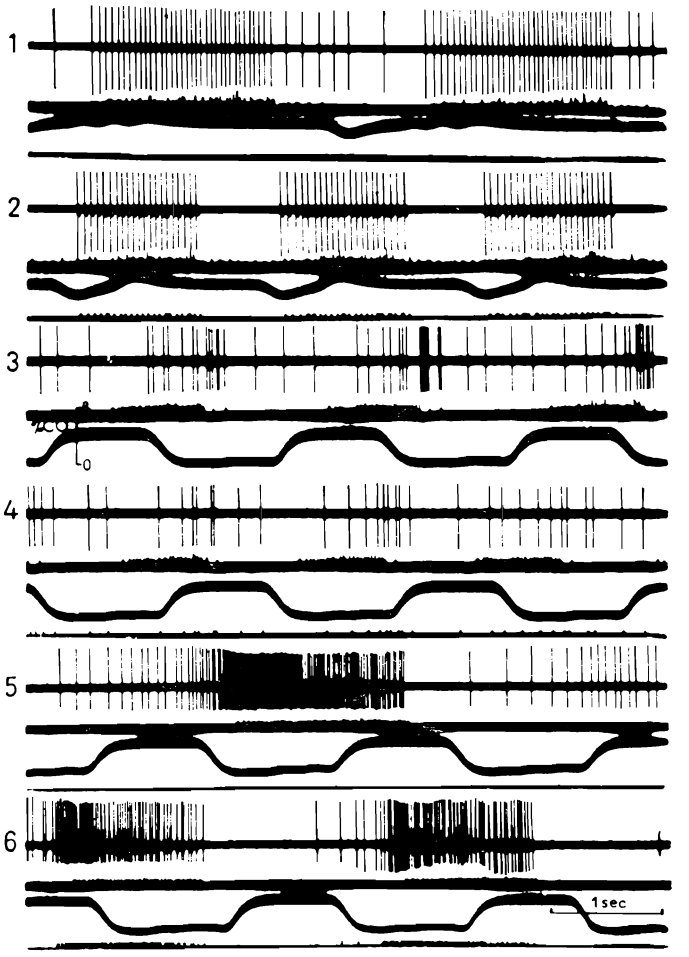

Fig. 7. Effects of "self-stimulation" (*see* text) on the discharge of a medullary inspiratory unit and phrenic n. activity under various experimental conditions. Traces from top to bottom: unit discharge, phrenic n. activity, end-tidal CO_2%, stimulus marker. *1*, control run, vagotomized, spontaneously breathing rabbit; *2*, during self-stimulation triggered from the medullary neurone; *3*, control run, artificial ventilation (the same unit); *4*, during self-stimulation; *5*, control run after an i.v. injection of 3 ml of chloralose-urethan (same unit); *6*, during self-stimulation. Note marked changes in the firing pattern of the neuron under different control conditions.

activity and end-tidal CO_2 percentage were recorded continuously. Arterial PO_2 and PCO_2 were measured periodically by means of Astrup micromethod (Radiometer). In spontaneously breathing animals tidal volume and respiratory rate were also continuously recorded (Godart Pneumotachograph). Hypercapnia was produced by giving a 7% CO_2

mixture in air during 2 min; this procedure increased $PACO_2$ by 15 mm of mercury (average). Hypocapnia was produced by increasing the frequency of the respiratory pump until end-tidal CO_2% dropped below 2%; this corresponded to a lowering of $PACO_2$ by 10 mmHg (average) as compared with the control values.

1. Inhalation of 7% CO_2 mixture elicited only one consistent effect in lightly anaesthetized, artificially ventilated rabbits — a decrease in the

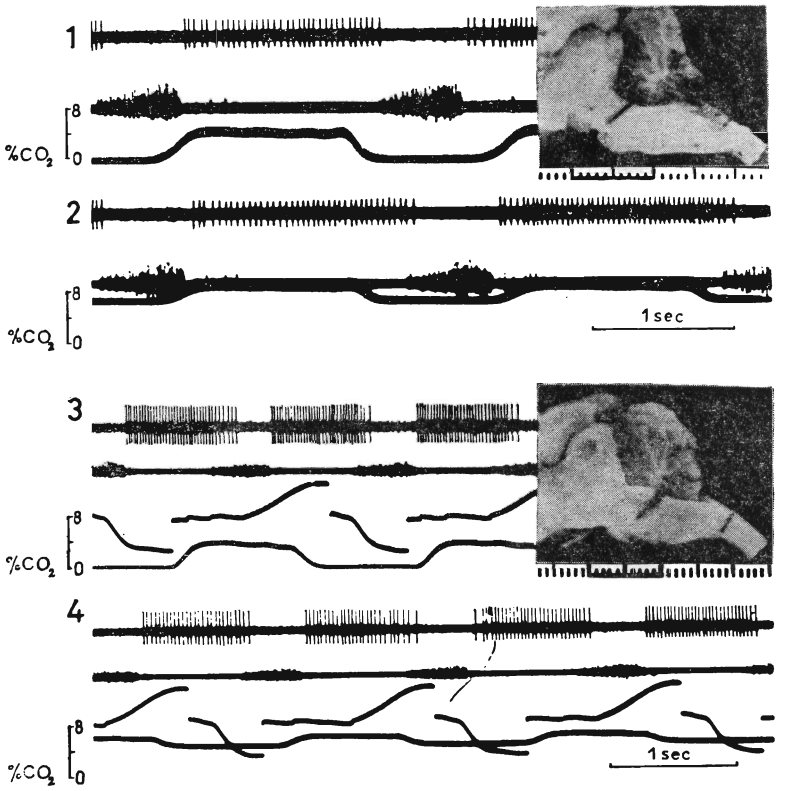

Fig. 8. Effects of CO_2 on the discharges of expiratory pontine units and phrenic n. activity in lightly anaesthetized, vagotomized and artificially ventilated rabbits. Traces from top to bottom (in *1* and *2*) unit discharges, phrenic n. activity and end-tidal CO_2%: (in *3* and *4*) unit discharges, phrenic n. activity, tidal volume and end-tidal CO_2%. Insert indicates the site of recording. *1*, control run; *2*, during 7%CO_2 inhalation (2nd min); *3* and *4*, another rabbit, records like in *1* and *2*.

central respiratory frequency (Fig. 8) both with vagi intact or cut. Under surgical anaesthesia a small but statistically significant increase in the activity of the expiratory units was observed. The other parameters did not change in a consistent way.

2. Hyperventilation in lightly anaesthetized, artificially ventilated

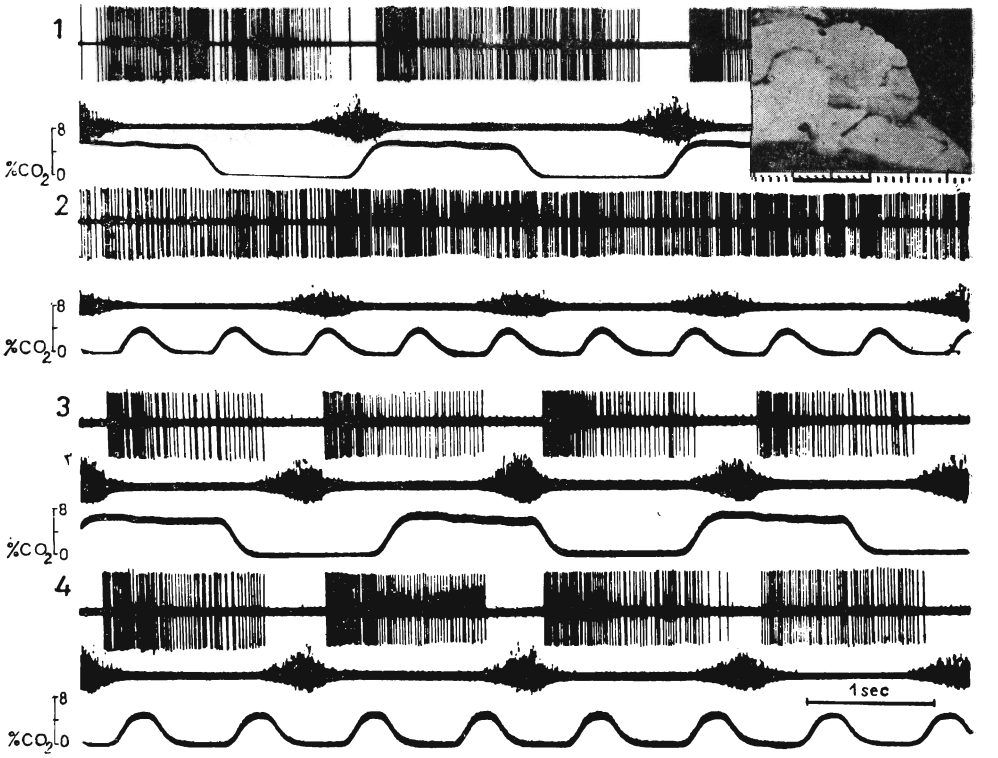

Fig. 9. Effects of hyperventilation on the discharges of a pontine expiratory unit and phrenic n. activity in lightly anaesthetized, artificially ventilated rabbit. Traces from top to bottom: unit discharges, phrenic n. activity and end-tidal CO_2%. *1*, control run (vagi intact); *2*, start of hyperventilation; *3*, control run after vagotomy; *4*, start of hyperventilation.

rabbits produced two consistent effects: continuous firing in one group of pontine expiratory units (located at the depth of 4 mm from the dorsal surface of the brain stem, 3 mm laterally to the midline and extending from 10 to 17 mm rostrally to the obex) and an acceleration of the central respiratory frequency. The former effect was abolished and the latter reduced by vagotomy (Fig. 9). The same procedure performed in surgically anaesthetized rabbits led to an inhibition of inspiratory activities (Fig. 10) and continuous firing of expiratory units (Fig. 11), both with vagi intact or cut. The other variables showed no statistically significant changes (*see* Gromysz 1971 for fuller discussion).

The rather obvious conclusion from these experiments was that the responses to hyperventilation and hypercapnia depend to a great extent on the experimental conditions. With vagi intact, the rhythm is always more or less locked to the respiratory pump; after vagotomy the respon-

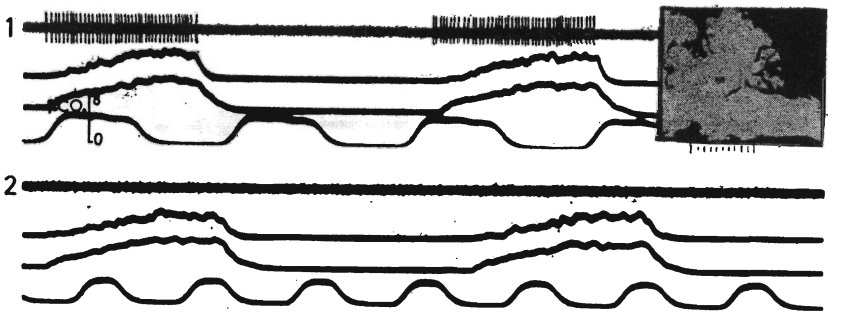

Fig. 10. Effects of hyperventilation on the discharges of a pontine inspiratory unit and phrenic n. activity in artificially ventilated rabbit under surgical anaesthesia. Traces from top to bottom: unit discharges, integrated activity of the left and right phrenic nerves and end-tidal CO_2%. *1*, control run (after vagotomy); *2*, 2nd minute of hyperventilation.

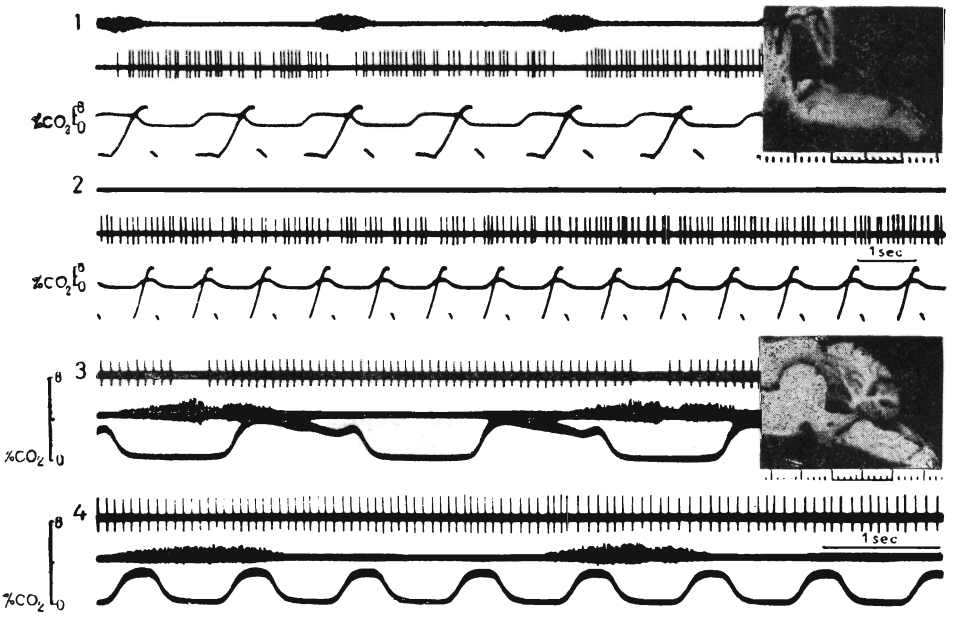

Fig. 11. Effects of hyperventilation on pontine expiratory units and phrenic n. activity in artificially ventilated rabbits under surgical anaesthesia. Traces from top to bottom: phrenic n. activity, unit discharges, end-tidal CO_2% and tidal volume in *1* and *2*, unit discharges, phrenic n. activity and end-tidal CO_2% in *3* and *4*. Inserts show the site of recording. *1*, control run (vagi intact); *2*, 2nd min of hyperventilation; *3*, control run (another animal, vagi cut); *4*, 2nd min of hyperventilation.

ses are modified by the absence of vagal information from the lungs and airways; under deep anaesthesia the vagus nerves seem to exert only their inhibitory functions (*see also* Bystrzycka and Huszczuk, this Symposium). In general, one could say that the experimental situation reminds the Heisenberg's "principle of indeterminancy".

3. On the other hand, the results obtained in spontaneously breathing rabbits were unequivocal. Under light anaesthesia all variables measured, i.e., minute ventilation, tidal volume, respiratory rate and frequency of discharges in expiratory and inspiratory units increased significantly (Fig. 12). Vagotomy reduced the response quantitatively; under deep

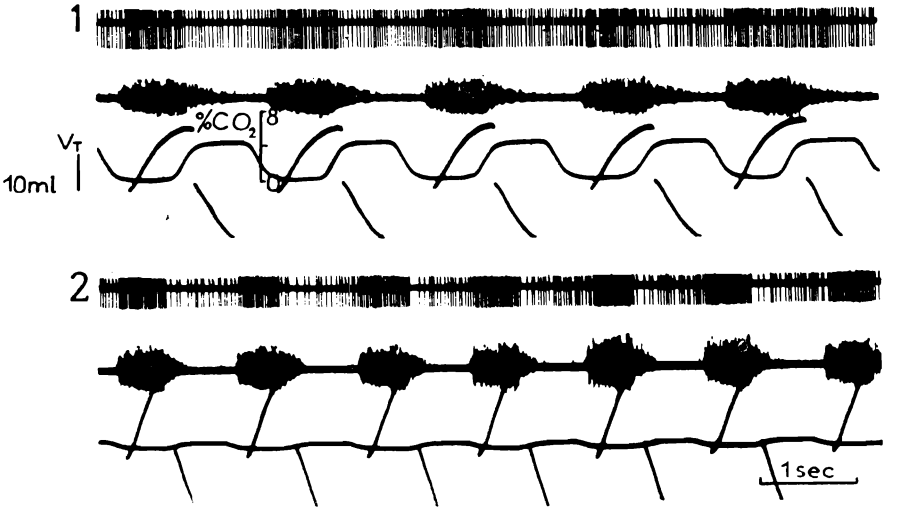

Fig. 12. Effects of 7% CO_2 on the discharges of a pontine expiratory-inspiratory unit, phrenic n. activity. V_T and respiratory rate in a spontaneously breathing, lightly anaesthetized rabbit. Traces from top to bottom: unit discharges, phrenic n. activity, tidal volume and end-tidal CO_2%. *1*, control run (vagi intact); *2*, 2nd min of CO_2 inhalation.

anaesthesia the only parameter that increased significantly was tidal volume. The results are summarized in a simplified way in Fig. 13.

The experiments have demonstrated that it is rather difficult to obtain an unequivocal neuronal reaction to low or high CO_2. In our opinion (*see also* Karczewski 1970*b*) the same neurone may respond differently to the same stimulus in different biological situations, or, in other words, there may be several "programmes" for every neuron rather than several types of neurons whose pattern of firing is strictly defined (Cohen 1970). The situation in spontaneously breathing animals may be even more complicated than in artificially ventilated ones. Apart

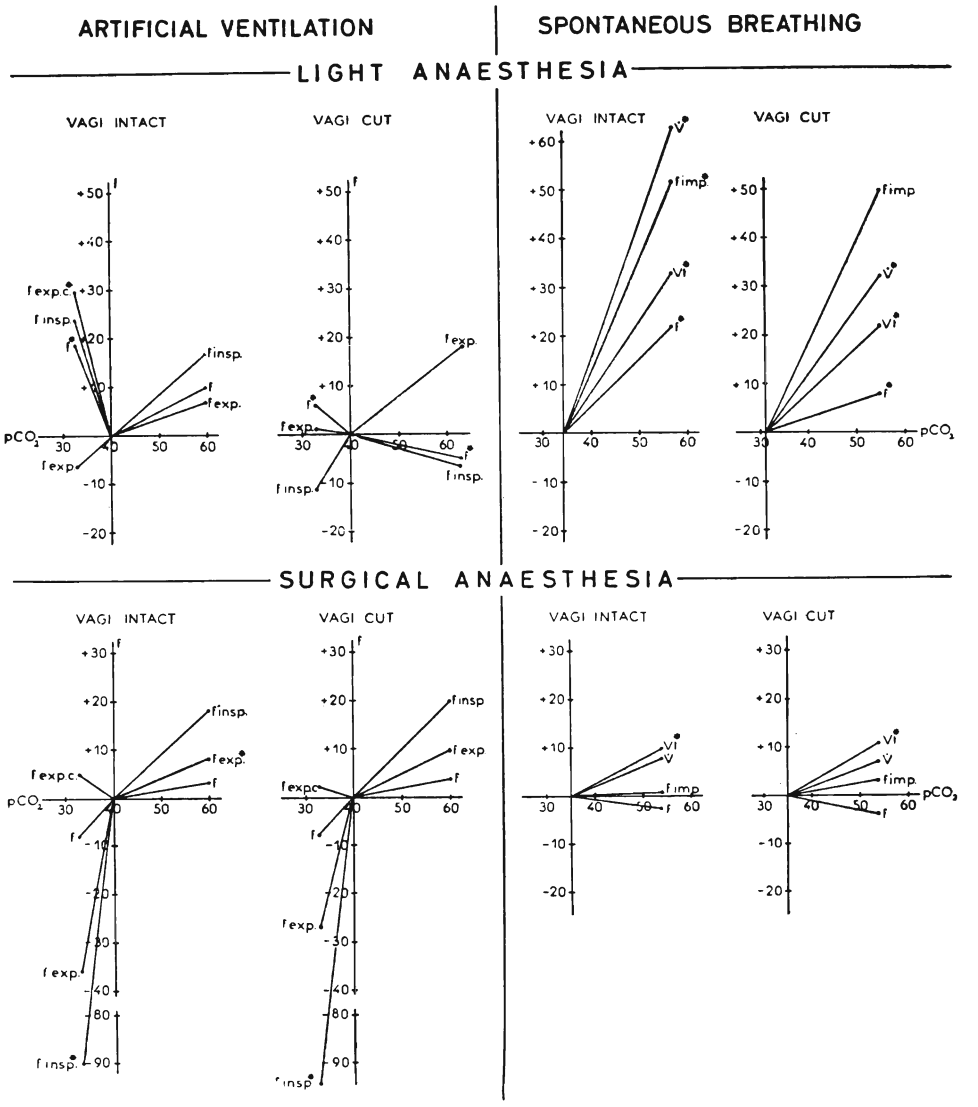

Fig. 13. Respiratory parameters plotted as mean changes (in per cent of the control) on the ordinates against $PaCO_2$ (absolute values) on the abscissae, in artificially ventilated and spontaneously breathing, lightly or surgically anaesthetized rabbits with vagi intact or cut. $f_{exp.c}$, frequency of expiratory discharges of pontine neurons responding to hyperventilation with continuous discharges before vagotomy; $f_{exp.}$, frequency of discharges in other expiratory pontine neurons; $f_{insp.}$, frequency of discharges of pontine inspiratory neurons; f, respiratory rate (or central respiratory frequency); $\dot{V}$, minute ventilation; V_T, tidal volume; $f_{imp.}$, frequency of discharges (inspiratory and expiratory) of pontine neurons in spontaneously breathing rabbits. Both types of neurons in these animals responded to CO_2 in the same way qualitatively and quantitatively. Statistically significant changes are marked by dots.

from the obvious technical difficulties, CO_2 is activating so many inputs to the brain stem and producing such a complex ventilatory response that interpretation of data from the point of view of neuronal mechanisms becomes hardly possible.

This led us to the first experiments in which we tried to combine the technique of "self-stimulation" with an inhalation of CO_2 in artificially ventilated rabbits. Figure 14 shows a representative experiment. Under steady ventilatory conditions, with vagi cut, a paralyzed and artificially

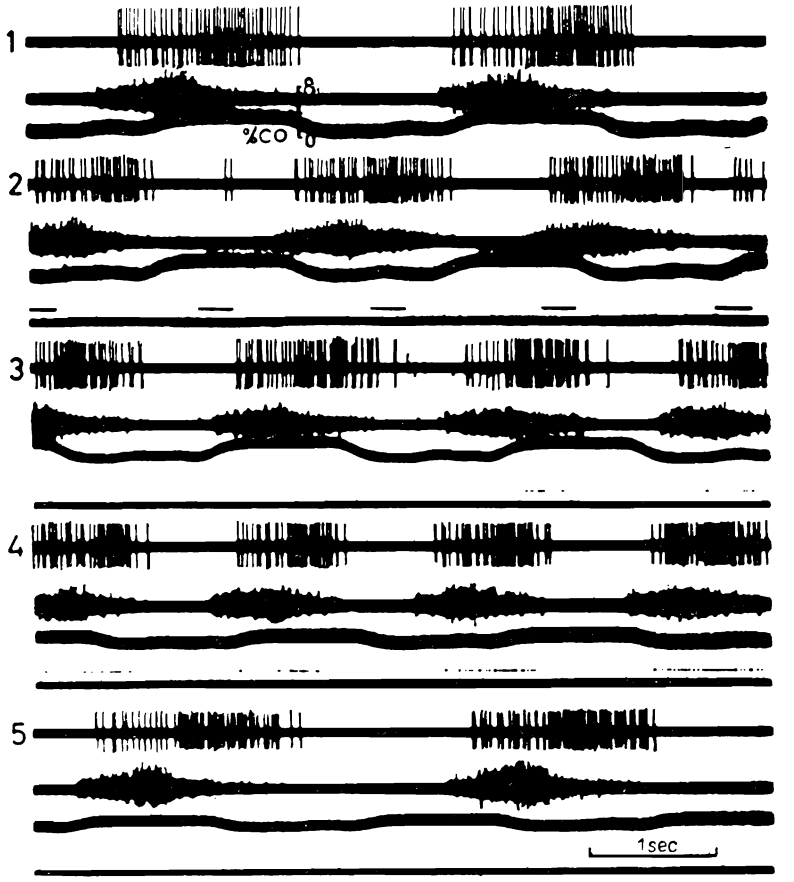

Fig. 14. Effects of "self-stimulation" and CO_2 on the discharges of a pontine inspiratory unit and phrenic n. activity in a vagotomized, artificially ventilated rabbit. Traces from top to bottom: unit activity, phrenic discharges, end-tidal CO_2%, stimulus marker. *1*, control run. *2*, rhythmic stimulation of the vagus nerve (ineffective). *3*, self-stimulation. *4*, self-stimulation combined with 7% CO_2 inhalation. *5*, self-stimulation switched off, CO_2 inhalation continued. Note that the increase in central respiratory frequency is biggest when vagal stimulation is combined with CO_2.

ventilated rabbit responds to CO_2 like a spontaneously breathing animal with intact vagi. The experiments seem to indicate that the presence of a rhythmic activity at the vagal sensory input is a very important component of the functional organization of the ponto-bulbar respiratory complex.

Although the mechanism of this phenomenon remains to be clarified, it seems that the attention should be focused on the group of pontine expiratory units that appear to respond directly to changes in the activity of the afferent fibres of the vagus nerve (*see also* Gromysz 1971). We hope that future experiments will support the hypothesis that this group of neurons may play an important part in transmitting and processing information from the lungs and airways and thus in modifying the pattern of activity of the whole respiratory control system.

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