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INSPIRATORY FACILITATORY AND INHIBITORY VAGAL INFLUENCES DURING APNOEA IN RABBITS

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Abstract. During hyperventilation apnoea in vagotomized, anaesthetized rabbits, paralyzed and artificially ventilated, the effects of electrical afferent stimulation of the vagus nerve on the provocation and inhibition of inspiratory activity were investigated. The experiments were repeated using hyperinflation or short-lasting inflation in non-vagotomized animals. It was found that the possibility of observing inspiratory facilitatory phenomena depended on the interrelationship between the frequency of impulses transmitted separately through the thick and thin myelinated fibres. The time constants of central summation of vagal information and the possibility of observation of the phenomena of inspiratory facilitation depended on the central respiratory drive changed by CO_2 and temperature.

INTRODUCTION

The studies presented here jointly (20, 27) dedicated to the problem of central integration of respiratory vagal information from the lungs are based, actually, on the results of fundamental studies by Breuer (5), Head (21) and Adrian (1). These papers described basic respiratory reflexes, in which the afferent information was transmitted along vagus nerve fibres from pulmonary receptors. All later works on the subject attempted to explain and to model the central mechanisms and routes of transmitting information in the vagal loop of regulation of the respiratory rhythm and volume. Among the most important is

the model of the central "off-switch" mechanism, switching over inspiration to expiration, whose threshold is reached by the central vagal activity (4, 10). It was found that the threshold of switching the phase of inspiration to the phase of expiration by the vagal activity decreases with the development of inspiratory activity (16, 17). There remain, however, many unanswered questions: 1) the functioning of the "off-switch" and generation of the alternating respiratory activity is not fully known; 2) is the processing of vagal information in the respiratory controller based solely on the frequency of impulses reaching the controller at a given moment-or is it also the result of temporal summation of signals steering the vagal regulatory loop? (32); 3) how can a simultaneous activation of several types of pulmonary receptors (which is most frequently the case) influence central processing of respiratory information at different levels of respiratory drive? 4) what are the mechanisms of inspiratory facilitation observed, sometimes, during stimulation of vagal input (15, 30). This work is an attempt to find answers to some of these questions.

METHODS

The experiments were carried out on rabbits, by the same methods as described in the first paper (27). Additionally, experiments were done on paralyzed rabbits ventilated artificially under halothane anaesthesia (0.7 vol%) with intact vagus nerves. During the experiments hyperventilation was performed with hyperinflations repeated periodically or using short-lasting inflation — ramp inflation with Medipan respirator (22, 35).

RESULTS

Electrical stimulation of the vagus nerve during hyperventilation apnoea

During hypocapnic apnoea a continuous tonic activity was often observed in some phrenic motoneurones. These motoneurones provide a suitable background for the evaluation of both inhibitory and excitatory reflex effects of vagal stimulation. The effects were studied in terms of both discharge rate (f) of individual phrenic motoneurones and the amplitude of integrated activity of the phrenic nerve (INT.PHR.). It was observed that during hypocapnic apnoea LFS [1] caused a rise in

[1] LFS, low frequency stimulation (1–60 imp/s). HFS, high frequency stimulation (more than 90 imp/s). In the 60–90 imp/s range various effects were observed depending on the animal tested — stimulatory or inhibitory — because of that stimulation in this range was usually not applied.

the discharge rate of phrenic motoneurones. In those motoneurones which did not exhibit any tonic activity owing to low $PaCO_2$, the LFS evoked a tonic activity which increased with time. The activity appeared after a certain latency. The evoked activity decayed slowly with

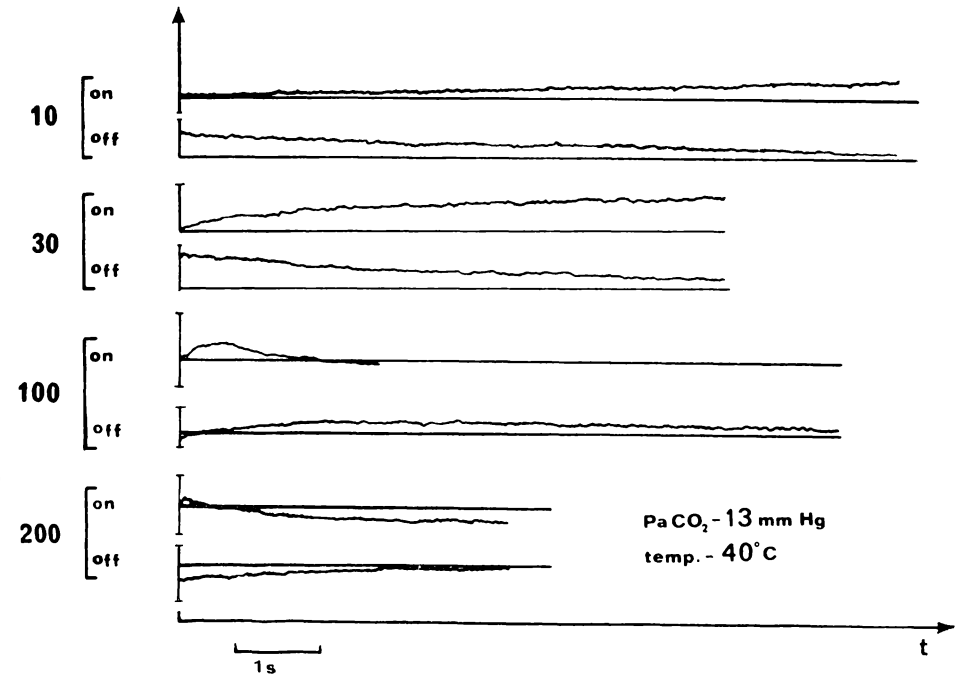

Fig. 1. Changes in integrated phrenic nerve activity (INT.PHR.) as a function of time, depending on the frequency of excitatory stimuli during hyperventilation apnoea in hyperthermia. The horizontal lines designate the INT. PHR. value. Attention is called to the fact that for the frequencies 100 and 200 imp/s after a transient rise in phrenic nerve activity an effect of inhibition of inspiratory activity appears. Experiment 3.9: temp. 40°C; $PaCO_2$, 13 mm Hg; BP, 70 mm Hg.

time when stimulation was discontinued. Within the range of 1 to 60 imp/s the latency of the appearance of activity decreased with increasing frequency of stimulation (6). The record of integrated total activity of the phrenic nerve (Fig. 1) shows that with increasing frequency of stimulation there is a continuous increase of inspiratory activity. The rate of rise grows with increasing stimulus frequency. With higher stimulus frequencies inhibition followed initial excitation (e.g. 100 and 200 imp/s, Fig. 1). In the situation when during apnoea the activity of the motoneurone was nil, and was induced only by LFS, a series of stimuli was applied at intervals lasting up to 20 s. It was found that the latency between the onset of stimulation and the appearance of

motoneuron activity was shorter if the stimulation was started soon after the extinction of previously induced activity (Fig. 2).

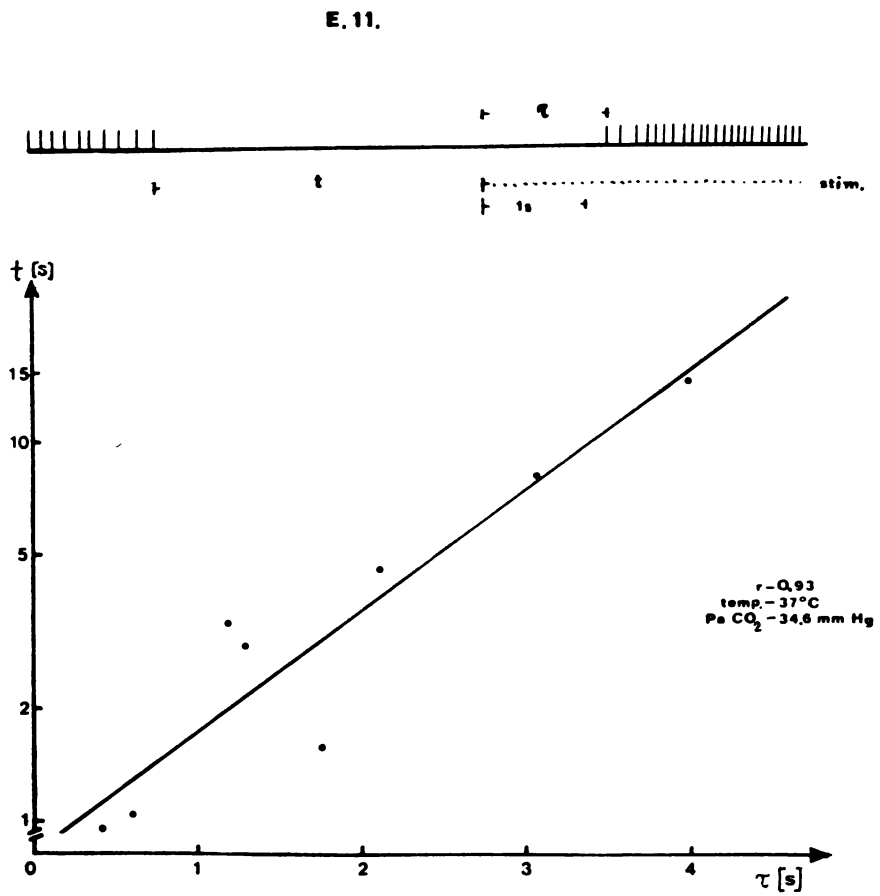

Fig. 2. Delay (τ) of induction of the activity of a single phrenic nerve motoneurone (upper curve) after starting vagus nerve stimulation (lower curve) depends on the time (t) passing after extinction of the activity produced by an identical stimulation earlier. The experiment was carried out during hyperventilation apnoea. The values on the axis of ordinates are expressed in a logarithmic scale, r, linear correlation coefficient; ⊢ ⊣, time or event marker.

That means that changes in excitability of the central respiratory system develop in the time when motoneurone activity is not recorded and can be expressed by the following formulas:

$$Y(t) = Y_s + (Y_o - Y_s) \exp(-k_1 t); \quad (1)$$

$t = 0$ at the time of LFS starting;

$$Y(t) = Y_o - Y_o - Y(x)) \exp(-k_2 t); \quad (2)$$

$t = x$ at the time when LFS was stopped, where Y(t) is the activity of the central respiratory system measured by INT.PHR. or *f*; Y_o, condition before stimulation; Y_s, condition established during stimulation expressed similarly by means of INT.PHR. or *f*; k_1, time constant during stimulation; k_2, time constant after stopping stimulation. The k_1 constant depends on the frequency of stimulating impulses and on $PaCO_2$, the k_2 constant depends here only on $PaCO_2$. Attention is called to the fact that when Y is measured with *f* it can assume negative values — which proves the arbitrariness of the accepted mathematical notation. This arbitrariness results even from the definition "central excitatory state" (see e.g. 12) for the respiratory system. If the motoneurone begins firing at the time $t_p > 0$, the motoneurone threshold can be defined as follows: the activity of a motoneurone begins when the central excitatory state reaches the value $Y(t_p)$. Similar types of experiments in the apnoea state were described in other papers (8, 14, 28).

This model of investigation of changes in the central excitatory state occurring during electrical stimulation of the vagus nerve could be applied also in the case of continuous tonic activity of phrenic nerve motoneurone observed during hyperventilation apnoea. During HFS application the activity of the motoneurone declines slowly in time, and after discontinuation of stimulation it returns slowly to the control state. When stimulation is repeated so frequently that the activity of the motoneurone has no time to return to its control state it is possible to observe a correlation between the frequency of discharges of motoneurones before stimulation and the time passing between the onset of stimulation and the complete inhibition of phrenic nerve motoneurones (Fig. 3).

Temperature effect on respiratory responses observed during electrical stimulation of the vagus nerve

During the investigations described in the previous chapter it was noticed that the rise of body temperature of the animals influenced the dynamics of respiratory responses to electrical stimulation of the vagus nerve.

In order to determine the effect of teperature on the response to vagal stimulation, other experiments were performed. As mentioned before, vagus nerve stimulation with high-frequency impulses (HFS) caused the prolongation of expiratory time (T_E). The more pronounced the prolongation, the higher was the frequency of stimulating impulses. The increased expiratory time, described frequently as expiratory excitation, is identified in this work as a temporal inhibition of inspirat-

ory generation. The correlation between the inhibition index (the ratio of the $T_E(S)$) value during stimulation (S) to the $T_E(C)$ value in control (C) determination immediately before the onset of stimulation) and the temperature was studied, maintaining a possibly steady $PaCO_2$ level

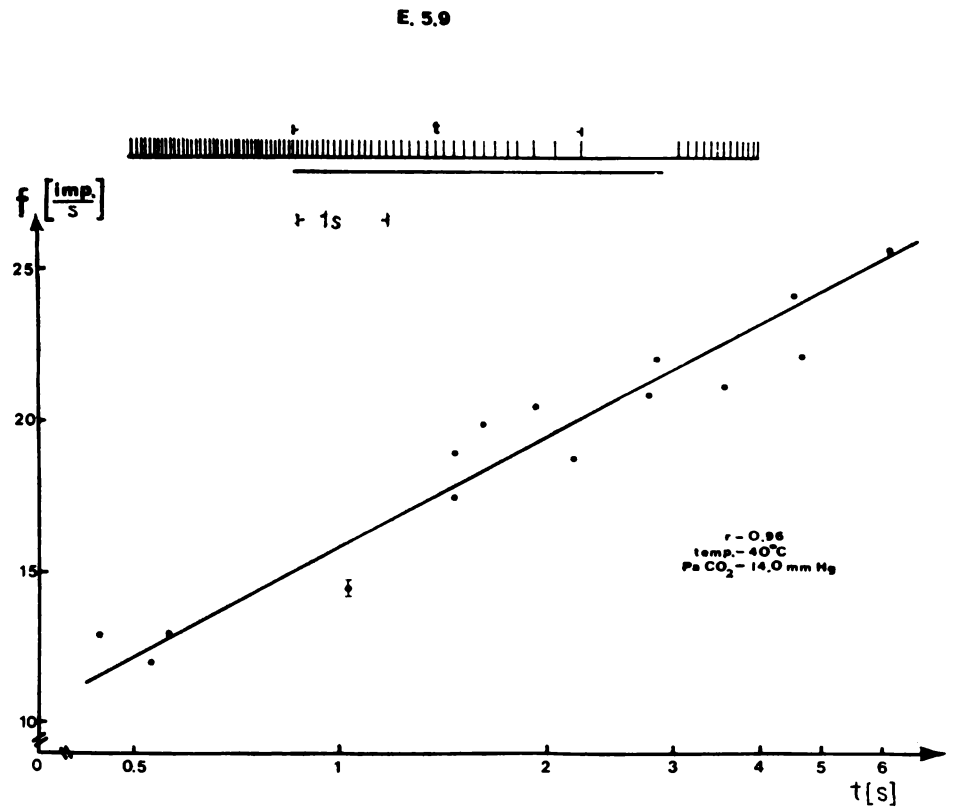

Fig. 3. The time (t) after which the activity of a phrenic nerve motoneurone is inhibited during stimulation with high-frequency stimuli (in this case: 90 imp/s) depends on the frequency of motoneurone discharges (f) just before starting stimulation. The variable of discharge frequency was obtained by repeating the same stimulation at small time intervals (stimulation was restarted before f returned to its control value); the lower value of f indicates a shorter time between two stimulations. r, linear correlation coefficient. The axis of ordinates is in logarithmic scale. Error of measurement is shown for illustration, as an example. ⊢ ⊣, time or event marker.

(Fig. 4). It was found that with increasing temperature the inhibition index decreased. This result could be shown as follows: for maintaining the inhibition index at a steady level the frequency of stimulation must be increased with the rise of temperature. It is interesting that the inhibi-

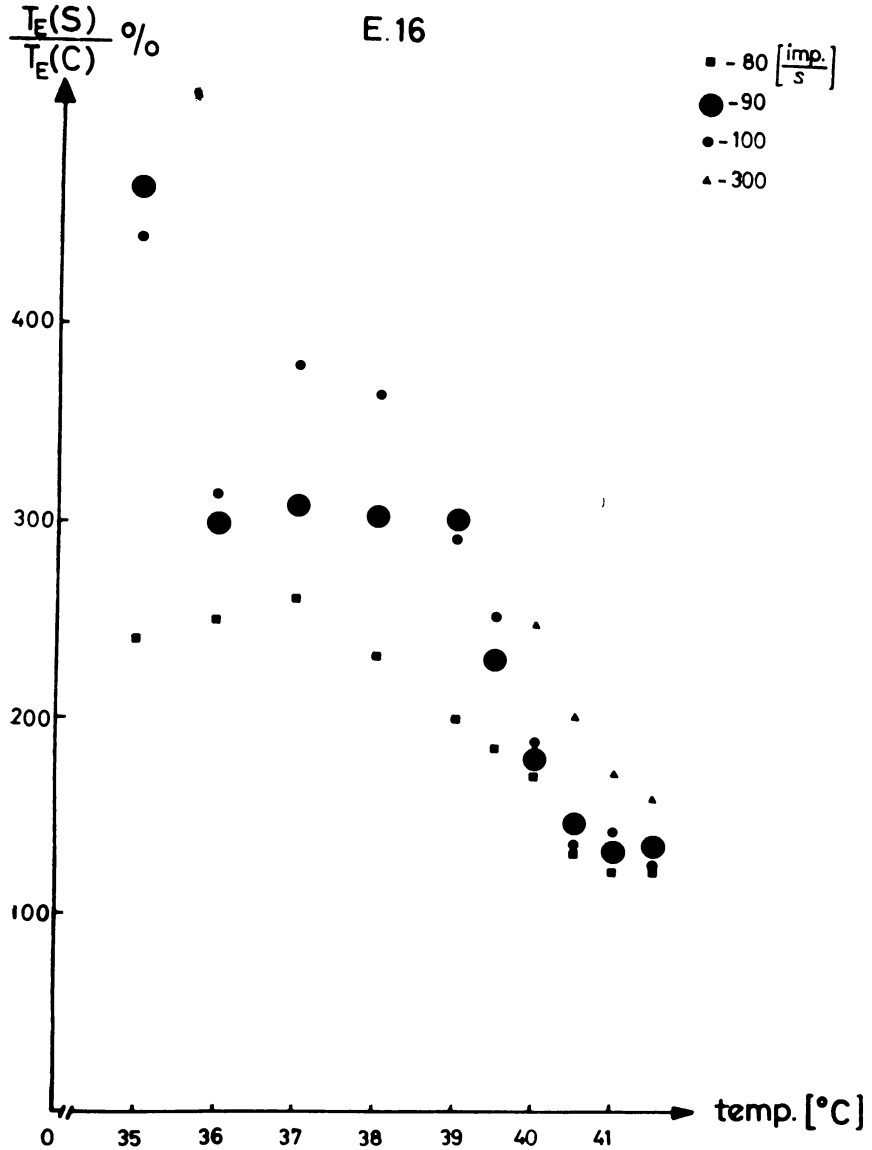

Fig. 4. Changes of the inhibition index ($T_E(S)/T_E(C)$) as a function of body temperature. $T_E(C)$, expiratory time before stimulation; $T_E(S)$, expiratory time during stimulation; Four frequencies exerting an inhibitory influence on respiration were used — 80, 90, 100, 300 imp/s. For the temperature below 39°C stimulation at 300 imp/s caused respiration inhibition with an index above 500%. Experiment 16: CO_2, 3.8+0.5%; BP, 90±5 mm Hg.

tion index shows quantitatively different changes in the temperature range below 36°C and above 39°C as compared to the range of temperatures around the normal value. It has been stressed earlier that not only the temperature but also a rise in $PaCO_2$ caused accelerated decay of the effects induced by $\alpha + \delta$ stimulation (6). It is worth

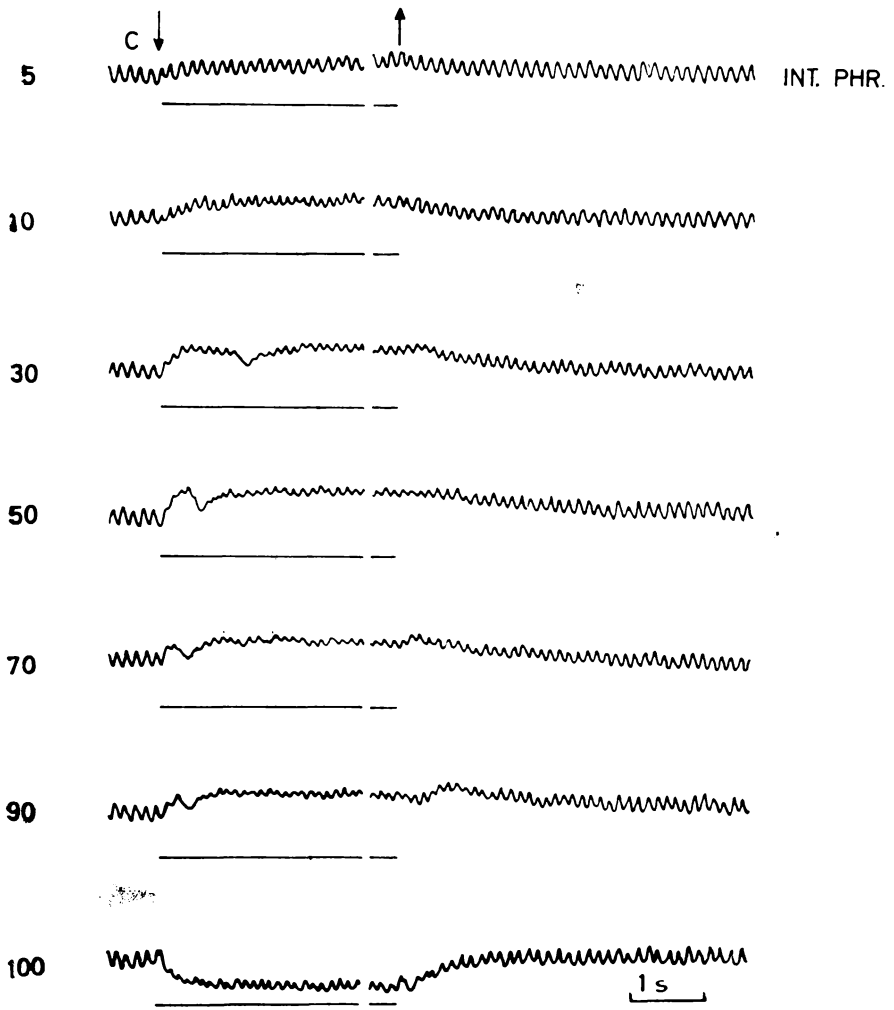

Fig 5. Thermally induced panting. Changes in the amplitude of integrated phrenic nerve activity (INT.PHR.) during stimulation (moments of switching the stimulation on and off are shown with arrows) in relation to the frequency of stimulation (from 5 to 100 imp/s) — records from top to bottom. C, control; Experiment 2: temp. 41°C, end tidal CO_2, 1.5%; BP, 90 mm Hg.

reminding here that Bystrzycka et al. (7) observed a decrease in the value of inhibition index of the inflation-triggered Hering–Breuer reflex with increasing CO_2 concentration in the alveolar air caused by reduced minute ventilation.

The effect of electrical vagal stimulation with variable frequency impulses was studied also in panting animals. The results were very similar to those obtained during hyperventilation apnoea (Fig. 5). Attention is called to the fact that phasic respiratory activity was present in that case (with late inspiratory motoneurones also active), but of low amplitude and during inspiratory excitation (see the lowest record in Fig. 5 where the level of integrated phrenic nerve activity was diminished by HFS).

Effects of short inflations or hyperinflation during hypocapnia in rabbits with intact vagus nerves

The irritant receptors (with thin myelinated fibres) are stimulated by hyperinflation, when high flow values are present (36). A number of experiments were done in which lung hyperinflation was applied during hyperventilation apnoea. During artificial ventilation using ramp inflation the stroke volume was increased for one stroke of pump piston thus increasing the flow ($\dot{V}$) with unchanged inflation time. It was observed that from a certain value (about 60 ml/s) it was possible to release a volley of inspiratory activity. The effects of hyperinflations are depicted in Fig. 6.

The time between the onset of hyperinflation and the appearance of phrenic nerve activity was inversely proportional to recorded flow value: the shorter the time, the higher the flow value (Fig. 6). Similarly, the evoked phrenic nerve activity was higher. The next inflation with control flow rate inhibited the inspiratory activity evoked in that way. These experiments are rather difficult to carry out because they are done at $PaCO_2$ values only slightly below the apnoeic threshold. It was found that after ventilation change the time of reaching a steady state during hypocapnia (i.e. time necessary to obtain reproducible responses during stimulation) was longer than during normocapnia. Similarly, with a slight decrease of $PaCO_2$ the threshold for inducing phrenic nerve activity was significantly raised. In the experiments with electrical stimulation for low $PaCO_2$, the lowering of the threshold for evoking phrenic activity was obtained by raising body temperature. In the presently discussed experiments the effect of short-lasting inflation was also assessed without reducing the $PaCO_2$ value as during electrical stimulation, but by producing additionally a respiratory depression through administration of one- third of a normal dose of neu-

roleptanalgesics. Figure 7 shows the effect of high flow rates on phrenic nerve activity under the above-described conditions. Changes in inflations rate were obtained by reducing the duration of the ramp inflation but not its amplitude. In four successive records the evoked phrenic nerve activity in response to flow rates of 100 ml/s are pre-

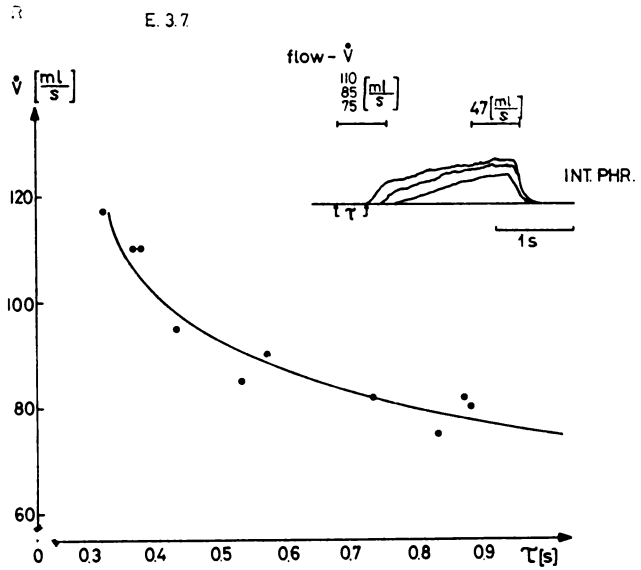

Fig. 6. Release of a volley of inspiratory activity of the phrenic nerve by hyperinflation during hyperventilation-induced apnoea. The animal was ventilated with a pump at a constant flow ($\dot{V}$) rate of 47 ml/s. For the duration of one pump stroke the flow (and thus the V_T, since the inflation time was unchanged) was increased. Above the $\dot{V}$ value of 70 ml/s it was possible to trigger a respiratory volley the earlier (τ) the higher was the value of $\dot{V}$. Three volleys released by hyperinflation at flow rates of 75–85 and 110 ml/s and then inhibited by "normal" inflation of 47 ml/s are shown as an example. Higher INT.PHR. amplitude and shorter delay correspond to higher $\dot{V}$ value.

sented. As shown in Fig. 7, the duration of evoked activity depended on the flow rates of a succeeding inflation, which begun after the same constant delay with respect to the first conditioning inflation. The shorter was the following inflation, the more rapidly it inhibited phrenic nerve activity (two middle curves). When the flow value of the next inflation was identical with that which had evoked inspiratory activity (lower record) the duration of the inspiratory volley was longer even than that obtained when stimulation was not followed by any inflation (upper record). It shows that the stimulatory effects of a short inflation during apnoea can be observed also during evoked developing inspiratory activity (26).

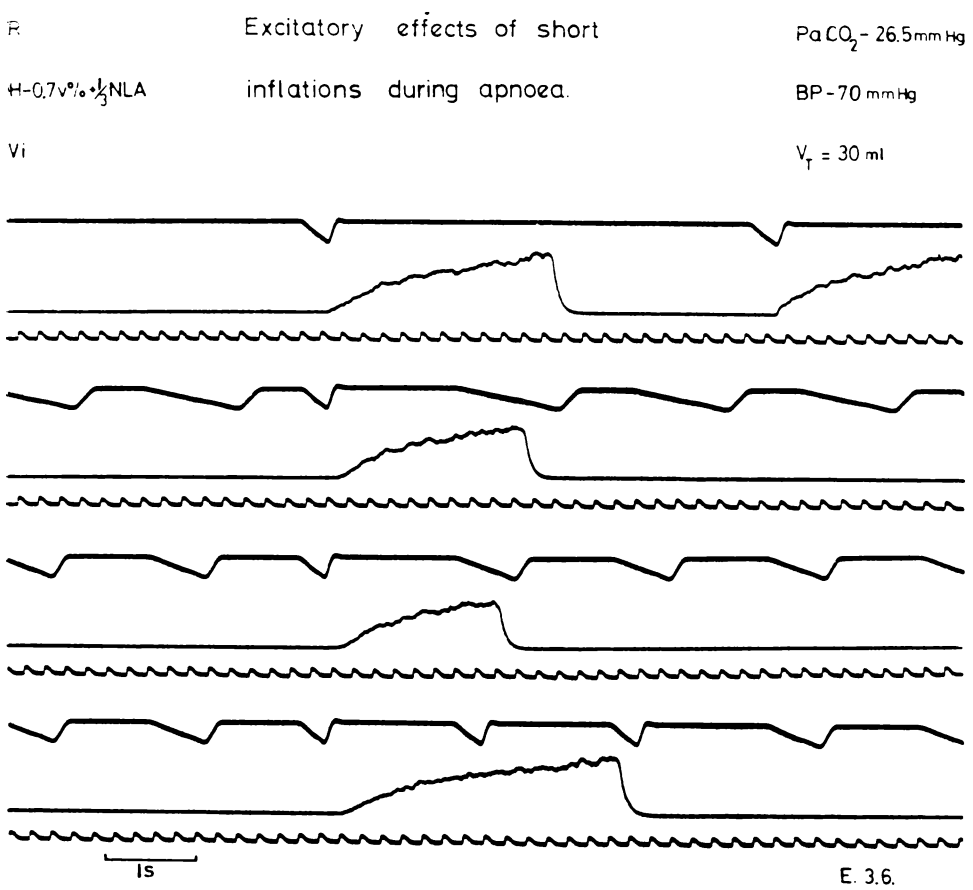

Fig. 7. Inflation of high flow value (100 ml/s) caused inspiratory activity observed in the activity of the phrenic nerve during apnoea (see text). Records from top to bottom: 1) respiratory volume signal from the pump, 2) phrenic-nerve integrated activity, 3) arterial blood pressure. From Karczewski et al. (26).

DISCUSSION

The results presented in this paper and in earlier works published by members of this team (6, 7, 23, 25, 33, 35) stress the fact that the central mechanisms of processing respiratory information transmitted along vagal fibres from the lungs are based on the phenomena of temporal and spatial summation. Although these phenomena have been very well studied at the level of single neurones, spinal reflex loops, and at higher levels of the central nervous system (37, 39), there are only scanty reports of the respiratory neuronal complex.

For that reason, before discussing our results, we shall try to base

our reasoning on the earlier described facts. One of the better known works on the regulation of rhythm and volume of respiration is that by Clark and von Euler (9). The authors demonstrated that inspiration is terminated at such values of V_T (tidal volume) which satisfy the equation $V_T \times T_I = \text{const.}$ (exact to constans). Assuming that $\dot{V}$ during inspiration is constant and that V_T is a linear function of INT.PHR. (13, 34), it appears that the Clark and Euler's relationship (9) is describing the steadiness of the summated phrenic nerve activity during inspiration (doubled triangle area). The results of other studies (35) indicated the necessity of viewing the mechanism regulating the duration and depth of inspiration from a different stand-point. It has been suggested that the steering signal in the loop of vagal negative feedback is not the activity of the pulmonary stretch receptors at a given time, but the sum of their activities during inspiration (35). In their paper Boyd and Maaske (3) stated that the parameters of inspiration depended on the following factors of electrical stimulation: duration of the volley of impulses, frequency of impulses in a volley, and the time of inspiration in which stimulation was started. Basing on the results of this work we can assume that the activity transmitted along vagal fibres is, after temporal summation, responsible for the duration of inspiration. With increasing inspiratory activity, the later vagal information reaches the respiratory controller, the stronger is the effect produced by it. This phenomenon is correlated with a progressive lowering of the threshold of the mechanism, switching the inspiration phase to the phase of expiration, as described by von Euler and Trippenbach (17). The results of the works of Feldman and Gautier (19), Younes et al. (40) and Cross et al. (11) suggest that the activity of pulmonary stretch receptors (PSR) is responsible for switching inspiration to expiration not only at the end of the inspiration phase, but also during its progress. Owing to difficulties in explaining the relationship between PSR activity and V_T and $\dot{V}$, divergencies have appeared in these works in assessing the influence of the inflation time on the activity of the phrenic nerve. Since the integrated vagus nerve activity is a function of both V_T and $\dot{V}$ (35), rejection of $\dot{V}$ influence on the observed effects will cause difficulties in the interpretation of results.

It is worth to recall here certain other investigations. Before the respirators controlled with biological signals have become available, (22) it was indispensable to define how a signal of phrenic nerve activity should be transformed for correlating it best with the value of the transpulmonary pressure. It has been found that this signal is summated activity transformed by an electronic integrator with a time constant

about 70–100 ms (13, 24). Now, returning to the problem, we could ask a similar question — what is the transformation mechanism of vagus nerve activity signal in the central respiratory controller. The activity of the vagus nerve integrated in a similar way as phrenic nerve activity is a function of the tonus of airways smooth muscles proportional to the transpulmonary pressure (34, 35). This signal of vagal activity fails, however to reflect satisfactorily respiratory rhythm changes evoked by vagal input change (35). It is assumed that the time constant of the central integration is several times higher and that signal transformation takes place in the same neuronal network which switches off inspiration to expiration without participation of vagal information. In this case we are not dealing with a simple addition of different influences (vagal and central), but with temporal and spatial summation of different inputs on single neurones. This phenomenon can be easily imagined on the basis of changes in activity of I_α and I_β neurones in response to vagal input (10). Another difficulty may be the fact that such summation is not a linear summation (see 10). The nonlinearity of this summation can be imagined best when the changes in

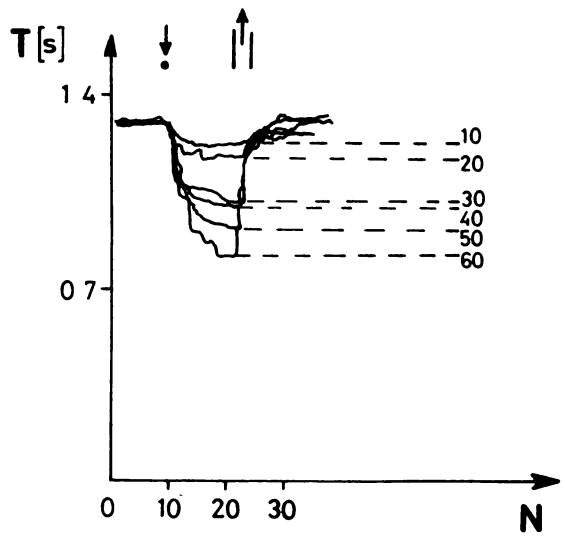

Fig. 8. Changes in the time of respiratory cycle from breath to breath during stimulation inspiration in at $\alpha+\delta$ (370 mV). The amplitude of the reaction (changes of T value from breath to breath) depended on the frequency of stimulating impulses (F.S.). The arrow pointing downwards, switching on; the arrow pointing upwards, switching off of stimulation. Experiment 22: temp. 39°C; CO_2, 4.2%; BP, 90 mm Hg. N, number of successive respiration cycles. 10, 20,..., 60, frequency of stimulation (imp/s).

the activity of phrenic nerve motoneurones after vagal nerve stimulation are analysed. Late recruited inspiratory motoneurones are less numerous than early recruited inspiratory neurones. Excitability of the late-recruited motoneurones is greater than that of early recruited inspiratory motoneurones (27). Their high sensitivity, the possibility of interconnections (38) (e.g. betwen early-inspiratory and late-inspiratory units) may be sufficient for observing changes in the rate of increase of integrated phrenic nerve activity occurring during changes of vagal output (positive feedback between vagus nerve activity and phrenic nerve activity (11, 23). This assumption has been confirmed by the unpulished results obtained by Huszczuk, suggesting that the possibility of observing positive feedback increase with increasing $PaCO_2$, when the number of activated late recruited inspiratory motoneurones is also increasing. This reasoning applies to the concept of transposition of the phenomena well known at the level of a single neurone to the properties of neuronal network. The basic qualitative modification of this concept is that a higher summation time constant is assumed to exist at the level of a network. In the paper of Cohen and Feldman (10) the graphs illustrating the regulation of expiration and depicting the effect of activities causing prolongation of T_E show a slow decay of the central inhibitory effects after discontinuation of stimulation. The rate of this decay is a function of the time constant of the leaky integration. Figure 8 shows the effects of temporal summation of the impulses transmitted along thin fibres. It demonstrates that the integration time constant was from 10–20 s. The information transmitted along thin fibres during expiration stimulates generation of a successive inspiratory volley. When continuous electrical stimulation of thin and thick fibres was applied during eupnea in inspiration, no excitatory effect was observed in the developing inspiratory phase. During breath-to-breath stimulation the inhibitory effects grow stronger (see Fig. 6 in the previous paper 20). However, if a short volley stimulating thin and thick vagal fibres is applied, prolongation of the inspiratory activity of the phrenic nerve is frequently observed in the first breath. Fallert and Spillmann (18) explained this fact as a result of postinhibitory rebound. In the experiments with electrical stimulation the frequency of stimulation of thick as well as thin myelinated fibres is identical. Actually, the firing rate of the activated irritant receptors during stimulation by hyperinflation is much higher than the firing rate of PSR. Since, probably, the sum of their activities during inspiration is responsible for the inhibitory effects, it appears possible that during brief inflation a short-lasting volley of high-frequency discharges transmitted along thin myelinated fibres can produce a stimulatory effect against a background of relati-

vely lower frequency of PSR discharges. This interpretation is supported by the results of studies in which the stimulatory effect of a brief inflation was found to increase after PSR activity blockade with SO_2 (15). Thus, the stimulatory effects observed in phrenic nerve activity would be possible in the case of a momentary disjunction of the stimulatory effects transmitted along thin myelinated fibres and the inhibitory effects passed along thick myelinated fibres. This disjunction may be caused by an excessive prolongation at a given moment of the stimulatory activity in relation to the remaining activity. The phenomenon of facilitation of the inhibitory activity by the activity transmitted along thin myelinated fibres (20) my be due to increased sensivity of the neuronal network of the central respiratory complex. When the activity passing along thin myelinated fibres becomes excessive, mementary stimulation of inspiratory activity generation may develop.

The above discussed hypothesis about the integrative basis of vagal (and possibly also of other input) activity transformation is founded on the integrative action of the central nervous system described long ago by Sherrington (37). The different summation time constants are a feature of neuronal networks participating in processing a given information. If the actual steering signals in the vagal control of respiration are the result of leaky summation of vagal activity with time constants comparable to the duration of the inspiratory phase and longer-continuous regulation may involve a series of two or three successive breaths. This conclusion is in agreement with the results of Priban (29) and Benchetrit and Bertrand (2) who have shown that a respiratory cycle is not an independent phenomenon.

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