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The Reflex Influence of a Group of Slowly Conducting Vagal Afferents on α and γ Discharges in Cat Intercostal Nerves*

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Summary. 1. The reflex influence of small vagal afferents on the α and γ activity in intercostal nerve filaments (CNFs) has been studied in cats. Selective activation of a group of vagal afferents has been achieved by injection of p-chlor-phenyl-diguanide into the right atrium.

2. About two seconds after the injection of the drug, the following simultaneously occuring phenomena have been observed:

a) Respiratory arrest near the end-expiratory level (functional residual capacity) lasting up to 30 sec.

b) Interruption of α activity and of rhythmic γ discharge both in inspiratory and exspiratory CNFs.

c) Decrease of tonic γ discharge frequency to approximately the inspiratory level in exspiratory CNFs and to the exspiratory level in inspiratory CNFs, respectively.

3. The same phenomena have been observed after intravenous injection of serotonine with the exception that towards the end of the apnoea signs of active expiration became occasionally apparent. Their separate cause is discussed.

4. The results suggest that stimulation of a definite fraction of slowly conducting vagal afferents in the cat may result in a temporary (partial) removal of supraspinal respiratory drive both to inspiratory and expiratory motoneurones. This is in contrast to results obtained after electrical stimulation of the fast conducting vagal afferents.

Key-Words: Vagal Reflex — Respiratory Motoneurones — Phenyldiguanide.

Schlüsselwörter: Vagaler Reflex — respiratische Motoneurone — Phenyldiguanid.

The existence of α and γ motor activity in intercostal nerves has been demonstrated first by Sears (1962) and by Eklund, v. Euler and Rutkowski (1963). Since then, much work on intercostal innervation has been published (for review, see v. Euler, 1966a, b; Sears, 1966a, b;

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Wellhöner, 1968). The respiratory system offers considerable advantages for an experimental approach to certain problems of motor integration, because its naturally arising supraspinal motor drive resists anesthesia. For a better understanding of the system, the study of reflex influences should be of particular value. Various reflexes have already been investigated with regard to their influence on the impulse pattern in intercostal nerve filaments (CNFs). As far as vagal reflexes are concerned, the influence of electrical stimulation of the vagus nerve has been studied by Eklund *et al.* (1964) and by Sears (1964a, b). With stimulus parameters appropriate to excite predominantly vagal fibres of highest conduction velocity (Steiner, 1955), both authors obtained an increase of discharge frequency in the expiratory CNFs; the discharge in inspiratory CNFs was decreased or even abolished. However, a selective activation of the slowly conducting afferents in the presence of fast conducting fibres has not been achieved in the vagus nerve by means of electrical stimulation. Eklund *et al.* (1964) with high intensity of stimulation obtained a variety of responses. Since then, the influence of slowly conducting vagal afferents on the impulse pattern in intercostal efferents has remained an open question. It has been made the subject of the work presented below.

Selective activation of a group of slowly conducting vagal afferents has been achieved by pharmacological excitation of receptors mediating the "Pulmonary Respiratory Chemoreflex" (PRC-reflex), so named by Dawes and Comroe (1954). If phenyldiguanide or some of its derivatives are used as stimulating drugs, only slowly conducting vagal afferents are excited while the activity in the fast conducting fibres from pulmonary stretch receptors remains essentially unaffected (Dawes, Mott and Widdicombe, 1951; Paintal 1953a, 1955; Wellhöner and Conrad, 1965). The nature of the diguanide-sensitive receptors and of the appropriate small vagal fibres has been investigated in detail by Paintal (1953a, b, 1954, 1957a, b, 1969a, b).

Material and Methods

The results reported below are based on experiments in 22 cats anesthetized with a mixture of chloralose (55 mg/kg) and urethane (200 mg/kg)—injected intraperitoneally—supplementary doses of 5 mg/kg chloralose and 20 mg/kg urethane were given during the experiments as needed. Pentobarbital anesthesia was not used because it caused more depression of the discharges in the CNFs, and also of the PRC reflex (Dawes and Mott, 1950; Wellhöner, 1961), than chloralose-urethane anesthesia. Additional ether anesthesia during the operative procedure proved to be usefull, as it minimized the danger of traumatic shock breathing, which might have rendered the animal unsuitable for further studies. Throughout the experiments, the temperatures in the rectum and in the paraffin pool above the ribs were controlled by means of Hg thermometers and they were regulated by

means of an infrared lamp from above and a heating pad from below. Circulatory stimulants and plasma expanders have not been used.

A tracheotomy was performed, a catheter of 0.4 ml dead space was passed down the left jugular vein into the right atrium. Both vagi were freed in the neck for a length of approximately 1 cm and loose ligatures placed around them to permit vagotomia later in the experiment; finally, the skin flaps in the neck were loosely clamped and the animal was placed on its left side.

The skin was opened in the axillary line and the musculature covering the Mm. intercost. ext. was incised, drawn back or partially removed until the Mm. intercost. ext. III—VII were freely exposed on the whole length of the costal interspaces. At this stage complete hemostasis was essential for an undisturbed recording procedure later on. The skin flaps were sewn up to form a pool which was filled with warm paraffin oil. Inspiratory and expiratory CNFs were now isolated following the methods given by Eklund *et al.* (1964) and by Sears (1964a).

Recording Procedures. The sagittal movements of the sternum were transmitted to a flat spring of high flexibility, the deflection of which was transduced by a strain gauge device into a proportional DC voltage. This signal was displayed on the lower beam of an oscilloscope and stored on magnetic tape.

The efferent activity in the CNF was led off with silver-coated platinum wires of 0.15 mm diameter, preamplified, displayed on the upper beam of the oscilloscope, and stored on tape. The bandwidth of the preamplifier was set between 80 Hz and 10 kHz, both channels of the tape recorder in the FM-mode and the tape speed at 15 inch/sec. On play back the amplitude damping was 5% at 1.8 kHz.

Films were taken using the data stored on tape. The spike potentials were brightened by means of a circuit which does not introduce astigmatism. An impulse discriminator together with a frequency meter have been used for the selective display of the frequency of the small γ efferents.

Drugs. Atropine sulfat (Thilo), α-chloralose (Merck), chlorpromazine (Bayer), p-chlor-phenyldiguanide (Chemie Grünenthal), ethylurethane (DAB 7), procaine-HCl (Hoechst), and serotonine-creatininsulfat (Merck) have been used. p-Chlor-phenyldiguanide was chosen in place of phenyldiguanide because of its greater potency (Dawes and Mott, 1950). The drugs evoking the PRC-reflex were injected in relatively high concentrations (10^{-4} to 10^{-3} g/ml) using only small volumes of fluid (0.2—0.3 ml) for solution. For a differential block of fast and slow efferents by local anesthesia (Matthews and Rushworth, 1957a, b, 1958), after preliminary experiments with lignocaine (Eklund *et al.*, 1964) a 0.1% or 0.2% procaine solution has been used because the block seemed to be more rapidly reversible. The origin of the CNF was immersed in a few drops of the solution using a syringe with a small injection canula. After an effect has become apparent, the solution was withdrawn.

Results

p-Chlor-phenyldiguanide. About two seconds after the injection of the drug, apnoea occured. The sternum remained in a position identical with normal expiration (37 times) or slightly above this position (11 times). Only in one animal, where the drug has been given twice, after both injections the sternum rested in a more inspiratory position. These results confirm previous observations of Dawes, Mott and Widdicombe (1951), Paintal (1955) and Wellhöner (1961, 1964). The duration of the apnoea could be increased considerably by allowing the animal to

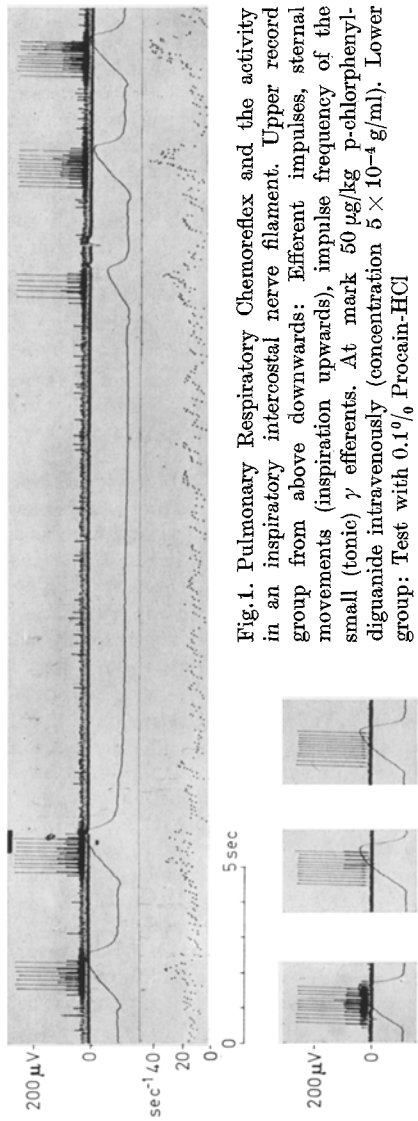

Fig. 1. Pulmonary Respiratory Chemoreflex and the activity in an inspiratory intercostal nerve filament. Upper record group from above downwards: Efferent impulses, sternal movements (inspiration upwards), impulse frequency of the small (tonic) γ efferents. At mark 50 µg/kg p-chlorphenyldiguanide intravenously (concentration 5×10^{-4} g/ml). Lower group: Test with 0.1% Procain-HCl

breath pure oxygen prior to the injection of the drug (Wellhöner, 1961). After the beginning of the apnoea, occasionally a small and slow inspiratory shift of the sternum has been observed simultaneously with an increase of γ activity in the inspiratory CNF. Tachyphylaxia occured if the drug was given again after less than 15 min. Simultaneously with the apnoea, all rhythmic activity in α and γ efferents was interrupted

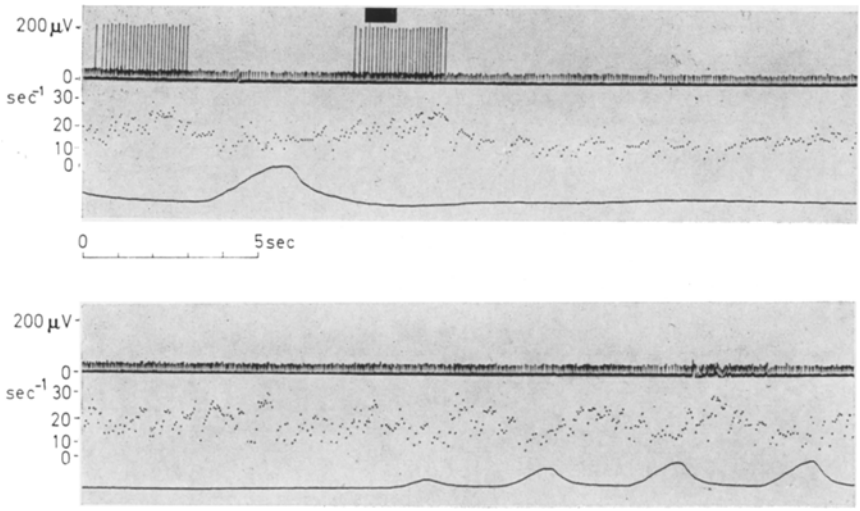

Fig. 2. Pulmonary Respiratory Chemoreflex and the activity in an expiratory intercostal nerve filament. In each record group from above downwards: Efferent impulses, impulse frequency of the small (tonic) γ efferents, sternal movements (inspiration upwards). Upper group: At mark 50 μg/kg p-chlor-phenyldiguanide intravenously (concentration 10^{-3} g/ml). Lower group: End of reflex respiratory arrest

(Figs. 1 and 2). The discharge in the α efferents both from inspiratory and exspiratory CNFs ceased completely, as did also the discharges of intermediate amplitude (attributed to "rhythmic γ" efferents by Corda *et al.*, 1964, 1966). Occasionally, "rhythmic γ" efferents have been observed, which resemble the "tonic γ" efferents with smaller spike amplitude in that they are active throughout the respiratory cycle. They too became silent during the apnoea. Only the "tonic γ" efferents both from inspiratory and expiratory CNFs were left with a continuous discharge of low frequency throughout the duration of the respiratory arrest. In no case was an interruption of the tonic activity observed. Its frequency in expiratory CNFs was identical with or slightly above the frequency measured at the height of inspiration, i.e. with the normally occuring minimal frequency. The modulation of the "tonic γ" discharge reappeared simultaneously with the first breath at the end of the apnoea, the "rhythmic γ" efferents followed shortly after, then the inspiratory α efferents came into play. The expiratory α efferents reappeared only after a minute or even a longer time. This recovery sequence closely resembles that following an apnoae induced by hyperventilation (Sears, 1964a).

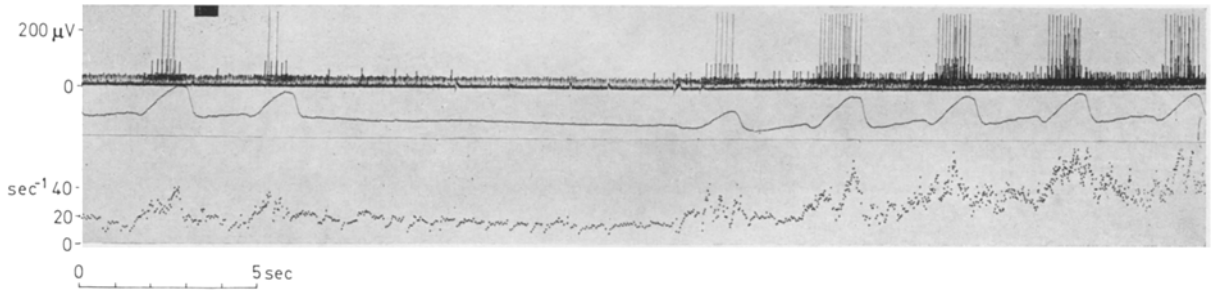

Fig. 3

Fig. 3

Pulmonary Respiratory Chemoreflex and the activity in an inspiratory intercostal nerve filament (which is identical with the filament from Fig. 1). At mark 20 µg/kg serotonine intravenously (concentration 2×10^{-4} g/ml)

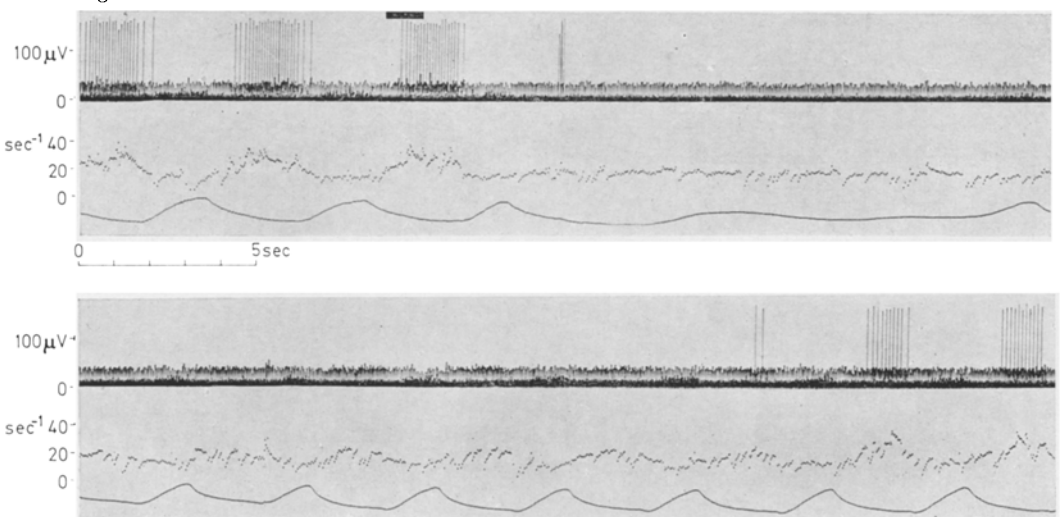

Fig. 4

Fig. 4

Pulmonary Respiratory Chemoreflex and the activity in an expiratory intercostal nerve filament. In each record group from above downwards: Efferent impulses, impulse frequency of the small (tonic) γ efferents, sternal movements (inspiration upwards). Upper group: At mark 50 µg/kg p-chlor-phenyldiguanide intravenously (concentration 10^{-3} g/ml). Lower group: End of reflex respiratory arrest

Serotonine. The excitation of slowly conducting vagal afferents in the vagus nerve by serotonine has been demonstrated by Paintal (1955). With this and other evidence, the changes in respiration observed in the cat after intravenous injection of serotonine have been explained as being components of a PRC-reflex. However, an excitation also of fast afferents from the pulmonary stretch receptors has been described by Schneider and Yonkman (1953). According to Mott and Paintal (1953) this excitation is indirect in that it is the consequence of a serotonine-induced bronchoconstriction. Nevertheless, the apnoea in the cat observed by many authors after the injection of serotonine might in part be due to a Hering-Breuer reflex. In that case, the expiration should be active. This has been investigated in the present work. It was found that sternal movements as well as the pattern of efferent discharge both in inspiratory and expiratory CNFs resembled closely the results obtained after the injection of the diguanide (Figs. 3 and 4). Occasionally, however, signs of an additional active expiratory component were observed towards the end of the respiratory arrest.

Chlorpromazine. Chlorpromazine was found by Wellhöner *et al.* (1960) to meet all the requirements formulated by Dawes and Comroe (1954) for a drug inducing the PRC-reflex. A non-active character of the reflex apnoea should therefore be expected. This was confirmed by the present experiments: During the reflex, sternal movements and patterns of impulse activity in the CNF were very similar to those observed after the injection of the diguanide, although chlorpromazine was considerably less potent as a reflex inducing drug. Unlike diguanide and serotonine, however, chlorpromazine has a second action which was not immediately apparent but developed some minutes after the injection. A strong and long-lasting decrease of the activity in the "small tonic" γ efferents could then be observed. With a dosis of about 1 mg/kg, their activity might even be abolished for 10 min or longer.

Atropinization and Bilateral Vagotomia. The common reflex effects of p-chlor-phenyldiguanide, serotonine, and chlorpromazine described above were not affected by previous application of atropine 0.5 mg/kg or 1 mg/kg. The tendency for active expiration after serotonine injection was reduced by atropine. Bilateral vagotomia abolished the reflex effect of p-chlor-phenyldiguanide, serotonine, and chlorpromazine completely.

Discussion

The main result consists in the fact that unlike the apnoea in active expiration induced by electrical stimulation of large diameter fibree (Eklund *et al.*, 1964; Sears, 1964a, b), the apnoea induced by chemicas stimulation of small diameter fibres was neither active in expiration or

inspiration; it occured at a lung capacity resulting from the equilibrium between elastical and gravitational forces in the absence of respiratory muscular forces. This capacity was identical with or slightly greater than the functional residual capacity. In the present work the absence of active expiration during the apnoea is indicated not merely by the cessation of α discharge in the expiratory CNFs, but even more convincingly by the frequency response of the continuously discharging expiratory γ efferents. The disappearance of only the rhythmic modulation of the γ discharge during the PRC-reflex is a strong indication for the disappearance of the supraspinal expiratory drive. It would be less justified to draw this conclusion merely on the basis of the interrupted α discharge, because its cessation might be due alternatively to a strong active inhibition of α motoneurones. This inhibition would then be superimposed on the still functioning periodic excitatory drive. As to be seen from Sears (1966b), such an inhibition would shift the membrane potential in negative direction and the critical firing level no longer would be reached even at the height of the depolarization due to the rhythmic excitation. In the present work the frequency of the γ discharge does not indicate a strong supraspinal inhibition. However, with the limited accuracy of this criterion one cannot be sure about a weak inhibition on α motoneurones. Investigations with intracellular microelectrodes would be required to answer this question more definitely. Two observations from other authors are relevant to this problem: 1. According to unpublished work from Deshpande and Devanandan[1] cited by Paintal (1969b), a decrease of monosynaptic reflex response of hind limb flexor and extensor muscles has been observed after injection of phenyldiguanide. This has been explained as being due to an inhibition of α motoneurones. 2. Ginzel *et al.* (1968), and Ginzel and Eldred (1969a, b) reported that phenyldiguanide reflexly depresses fusimotor activity recorded from L 7 or S 1 ventral root filaments. This effect was resistant to atropine, but was abolished by bilateral vagotomia. In the decerebrated cat, after injection of phenyldiguanide they observed relief of decerebrate rigidity which "exceeded in duration the brief reflex apnoea, bradycardia and hypotension" produced by this substance.

It is not a matter of course that the reflex apnoea after some drugs is neither active in inspiration or expiration. Quite the contrary might be expected on the basis of foregoing investigations. Firstly, electrical stimulation of fast conducting vagal afferents leads to active expiration, as already mentioned. Secondly, electrical stimulation of all vagal afferents in the cat leads to active inspiration (Steiner, 1955). This is

1 Note added in proof: This work has been published now in J. Physiol. (Lond.) **206**, 345–357 (1970).

explained by Steiner as being mainly due to the reflex action of the slowly conducting afferents. Insofar, his explanation is in accordance with the concept of Wyss. This concept has been first formulated on the basis of experiments performed in the rabbit by Wyss and Rivkine (1950). It has been developed and secured later on in a series of pioneering experiments (for review, see Wyss, 1964). On the basis of this concept one has no difficulties to explain the action of the diguanide in the rabbit, where a shift in inspiratory direction is induced by adequate electrical stimulation (Wyss and Rivkine, 1950) as well as by injection of phenyldiguanide (Dawes, Mott and Widdicombe, 1951; Homberger, 1968; Karczewski and Widdicombe, 1969). In the cat, however, phenyldiguanide produces apnoea, but not inspiration (Dawes, Mott and Widdicombe, 1951; Wellhöner, 1961, 1964; Homberger, 1968), while electrical stimulation still results in inspiration (Steiner, 1955). No explanation will be forwarded in the present work because on the basis of the available evidence this would be speculative. However, the experiments reported above rule out one possibility: In the cat, the respiratory arrest after injection of the diguanide derivative is certainly not the result of a competition between actively innervated inspiratory and expiratory muscles and very probably not the result of a competition between activation and inhibition on the spinal level.

Serotonine. A reflex apnoea in the cat after intravenous injection of serotonine has been observed by many authors (Reid and Rand, 1951; Page, 1952; Comcoe *et al.*, 1953; Mott and Paintal, 1953; Fastier *et al.*, 1959); extensive studies have been made by Kottegoda and Mott (1955) and Westermann (1958). Mott and Paintal (1953), Kottegoda and Mott (1955) and Paintal (1955) demonstrated that the respiratory arrest in the cat observed after intravenous injection of serotonine is due to an activation of the PRC-reflex. The results of the present work produce additional evidence for their conclusion from another point of view in that an impulse pattern comparable to that after injection of the diguanide has been observed in the CNFs. Occasionally, however, signs of active expiration have been registrated towards the end of the respiratory arrest. This is explained as the consequence of the simultaneously occuring bronchoconstriction, which has been described for serotonine by Comroe *et al.* (1953). The bronchoconstriction activates pulmonary stretch receptors (Schneider and Yonkman, 1953) and the inflow from the fast conducting afferents belonging to them leads to signs of active expiration in the CNFs. In addition, a direct action of serotonine on supraspinal structures as described by Westermann (1958) must be taken into consideration.

Chlorpromazine. A reflex apnoea in the cat after intravenous injection of chlorpromazine has been described by Maskowski *et al.* (1955), Feld-

man and Kidron (1957) and Wellhöner *et al.* (1960). The latter authors were able to demonstrate that the respiratory arrest was due to a reflex originating in the pulmonary vessels, that the reflex was mediated by slowly conducting vagal afferents, that afferents from pulmonary stretch receptors remained unaffected, and that chlorpromazine met all other criteria which had been formulated by Dawes and Comroe (1954) for a drug evoking the PRC-reflex. Chlorpromazine should then be expected to be active by evoking the PRC-reflex. In accordance with this expectation a non-active type of apnoea resembling the diguanide reflex has been demonstrated in the present work. However, beside the early reflex effect, chlorpromazine has a late effect on the small γ efferents, the discharge frequency of which decreased considerably or was even abolished. This observation parallels the results obtained by Busch *et al.* (1960) on the cat's hind limb.

Atropinization and Bilateral Vagotomia. Substances evoking the pulmonary respiratory chemoreflex are also known always to induce reflex bradycardia and hypotension (for review, see Dawes and Comroe, 1954). One might speculate that the changes observed in the discharge pattern of the intercostal efferents could be due in considerable part to hypotension. The reflex hypotension can be reduced with atropine, and this has been done in some of the experiments presented above. The results lend no support to the hypothesis that hypotension plays a considerable role in the creation of the changes in the intercostal efferent activity.—Another argument might be that the PRC-inducing substances evoke their effects on the intercostal efferent activity not via the vagus nerve, but by a direct supraspinal or spinal action. The abolishment of the reflex effects by bilateral vagotomia is a strong argument against such a hypothesis.

The idea to perform this work was born in a discussion with Dr. T. A. Sears, who also made valuable suggestions on the final form of the paper and amended the English. Dr. K. H. Ginzel and Prof. A. S. Paintal put some of their unpublished manuscripts at our disposal and discussed several topics with us.

Our thanks are due to all of them.

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