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THE RESPIRATORY ACTION OF PHENYL DIGUANIDE IN VAGOTOMIZED RABBITS

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Abstract. In anaesthetized rabbits phenyl diguanide not only stimulates breathing (rapid shallow breathing) by a vagal reflex from lung J-receptors, but also causes a similar response in bilateral vagotomized animals. Injection of the drug into different parts of the circulation indicates that the main non-vagal response of breathing arises from areas supplied by the vertebral arteries, presumably in the brain.

INTRODUCTION

It has been shown that PDG stimulates J-receptors in the lungs and that respiration is thereby changed (Paintal 1969, Guz and Trenchard 1971). In experiments using the anodal block technique on the vagus nerves to analyse the mechanism of action of phenyl diguanide, we found that there were changes in breathing caused by the drug after vagotomy. This suggested that the action of the drug was more complicated than had previously been thought, and we studied the problem further.

METHODS

The experiments were performed on rabbits (2.2–3.5 kg), anaesthetized with pentobarbitone sodium (40–50 mg/kg, intravenously). Tracheotomy and femoral artery and vein catheterizations were done routinely. Blood pressure, tidal volume and end-tidal CO_2% were recorded on a UV recorder (Honeywell), and in some experiments simultaneously on magnetic tape. Twenty rabbits were used in two experimental series.

1. Phenyl diguanide (100–200 μg) was injected into a femoral vein in rabbits with intact vagi, during anodal block of conduction (block of

conduction in myelinated A-B fibres), and with cut vagi. The anodal block method was described by Mendell and Wall (1964), and was used by Guz and Trenchard (1971) in their study of respiratory reflexes. We monitored the electrically stimulated compound electroneurograms of the vagus nerves, and used currents of 40–180 μa to block completely the A-B waves (including action potentials from pulmonary stretch and lung irritant receptors) leaving intact C waves (action potentials from J-receptors).

2. In the second series phenyl diguanide was injected into different parts of the circulatory system as follows: (i) intravenously [1]; (ii) into the left atrium, the catheter being tied into the atrium in animals with opened chest walls, which were subsequently closed to restore spontaneous breathing; (iii) into the ascending aorta, the catheter being passed through a brachial artery; (iv) into the descending aorta, the catheter being passed through a femoral artery; and (v) into the vertebral artery, the catheter being passed through a femoral artery. Injections at the sites were repeated before and after bilateral cervical vagotomy.

RESULTS

Group 1

The response of breathing frequency is shown in Fig. 1. The ordinate gives the frequency of breathing in the control condition, and the abscissa gives the frequency of breathing after injection of phenyl diguanide. The deviation from the "no change line" shows the direction and size of any change. Figure 2 gives the corresponding results for tidal volume.

Animals with cut vagi responded to phenyl diguanide with rapid, shallow breathing. The proportionate changes in frequency of breathing and tidal volume were similar in rabbits with intact vagi, blocked vagi and bilaterally cut vagi. These results raised the question as to where this respiratory response originated from? To answer this question we performed the second group of experiments.

Group 2

We first looked for stimulation of receptors (possibly nociceptive) in the cardiac muscle. By comparison of the responses to injection into the left atrium with those to injection into the ascending aorta we were able to exclude cardiac receptors (Fig. 3).

[1] We started with 100 μg of phenyl diguanide. In case of weak response the doses was increased to 150 μg and in a few experiments up to 200 μg. Then this full doses was repeated at all sites before and after vagotomy.

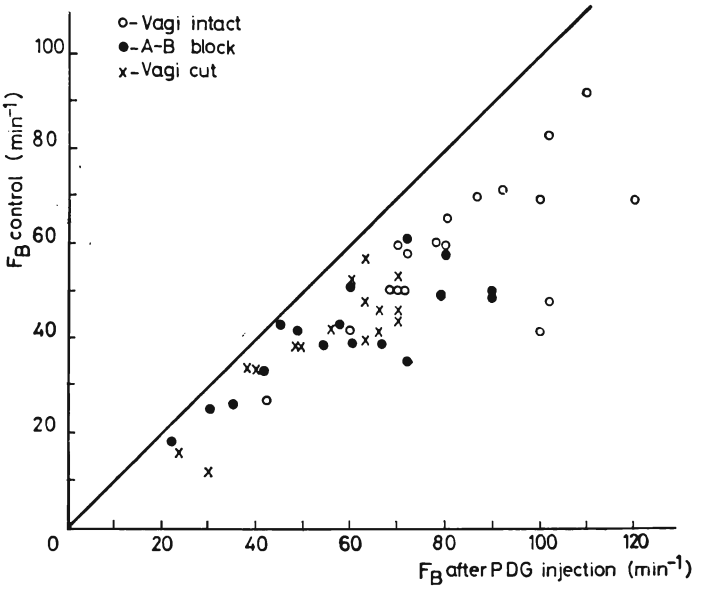

Fig. 1. Changes in frequency of breathing (F_B) after intravenous injection of phenyl diguanide. Ordinate, frequency before injection; abscissa, frequency after injection. The 45° line represents no change, and points to the right indicate an increase in frequency. Open circles, intact vagi; filled circles, anodal block of conduction in myelinated (A-B) vagal fibres; crosses, bilateral vagotomy.

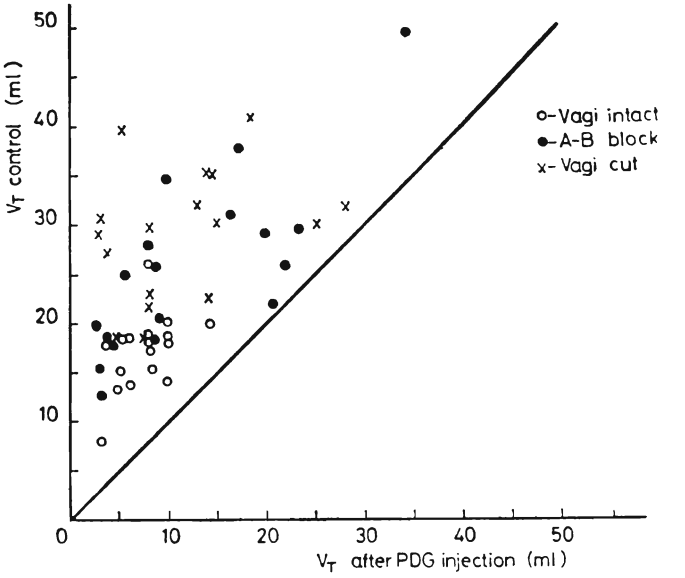

Fig. 2. As Fig. 1, but showing changes in tidal volume after intravenous injection of phenyl diguanide.

Similarly we excluded any contribution by gastric receptors or those supplied by the descending aorta since there was virtually no response when phenyl diguanide was injected into the descending aorta (Fig. 4).

The carotid body was a possible site of origin of the respiratory response. This could be eliminated by comparison of the pattern of breathing due to carotid body stimulation by potassium cyanide with that due to phenyl diguanide. The former caused deeper breathing, while phenyl diguanide caused rapid shallow breathing.

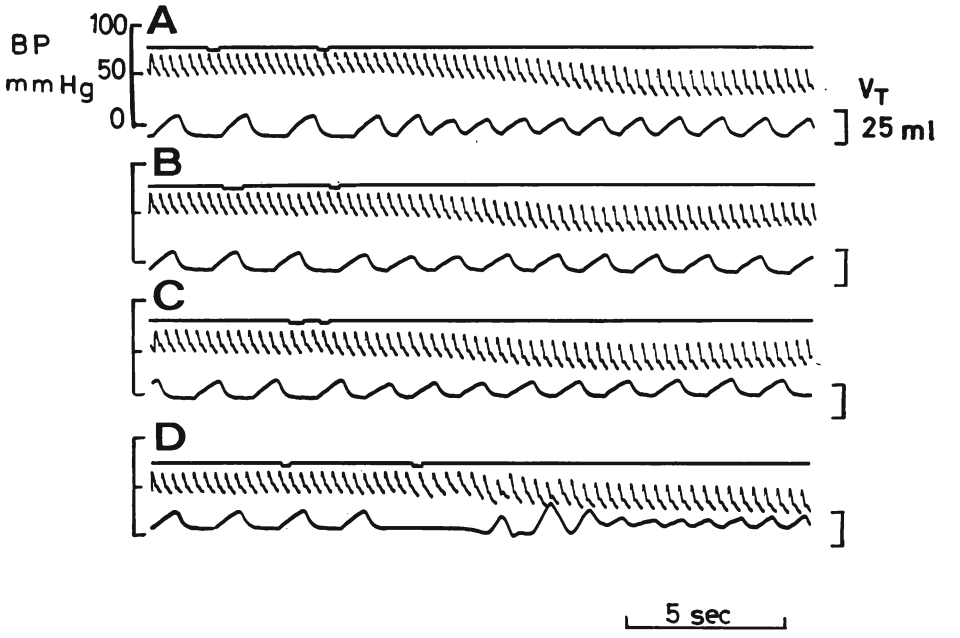

Fig. 3. Blood pressure (BP) and tidal volume (V_T) records. The top trace is a signal mark: phenyl diguanide injection at the first mark, wash in at the second. *A*, phenyl diguanide injected intravenously; *B*, into the left atrium; *C*, into the ascending aorta; and *D*, into a vertebral artery.

We next considered the possibility of a central nervous effect of phenyl diguanide. But before we designed experiments to test this question it chanced that in one experiment the femoral catheter was unintentionally passed into a vertebral artery, and phenyl diguanide was injected here. Of course we did not know where the tip of the catheter was until we did the post mortem after the experiment, but during the experiment we observed very strong respiratory and circulatory respon-

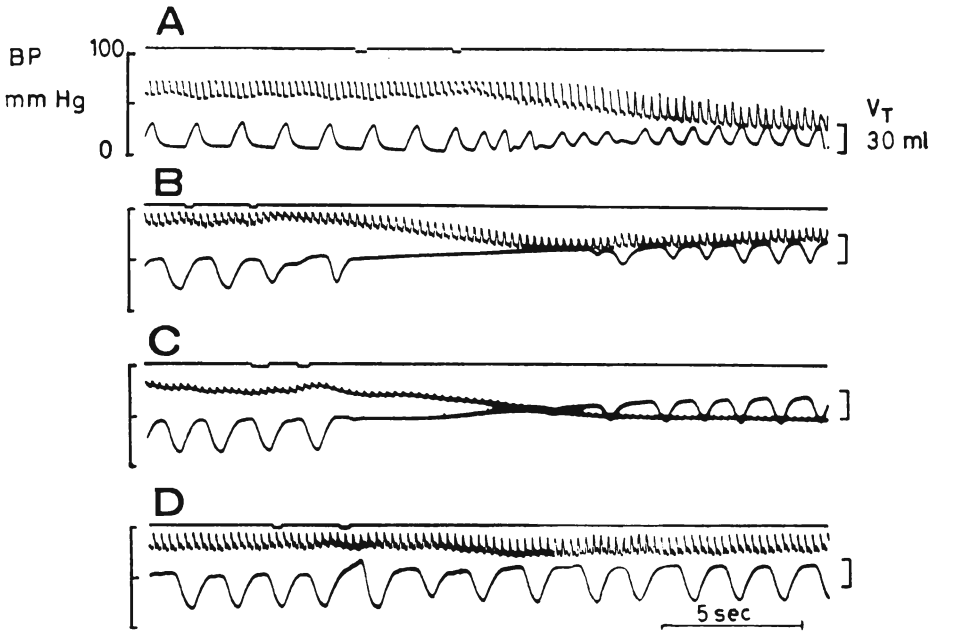

Fig. 4. Blood pressure and tidal volume records, and signal mark as in Fig. 3. *A*, phenyl diguanide injected into a femoral vein when vagi were intact; *B*, *C*, and *D*, after vagotomy: *B*, phenyl diguanide injected into a femoral vein, *C*, into the left atrium and *D*, into the descending aorta.

ses to injections of phenyl diguanide (Fig. 3 and 5). In two further experiments we deliberately passed the catheter into a vertebral artery in the same way. The respiratory response was reproducible and of a similar character both in rabbits with intact vagi and in vagotomized ones.

Table I contains a summary of the results of this experimental series.

TABLE I

Increases in breathing frequency after phenyl diguanide. Values are means and standard errors

Vagi	Intravenous	Left atrium	Descending aorta
Intact	**39.2±5.70 min^{-1} **78.2±14.45%	**17.3±4.57 min^{-1} **28.4±7.01%	*0.96±0.84 min^{-1} *0.25±0.48%
Cut	**16.7±5.24 min^{-1} **48.6±13.17%	**19.0±5.72 min^{-1} **48.8±11.09%	*0.50±0.28 min^{-1} *1.50±0.87%

* $p > 0.05$. ** $p < 0.001$, for difference between mean and zero change.

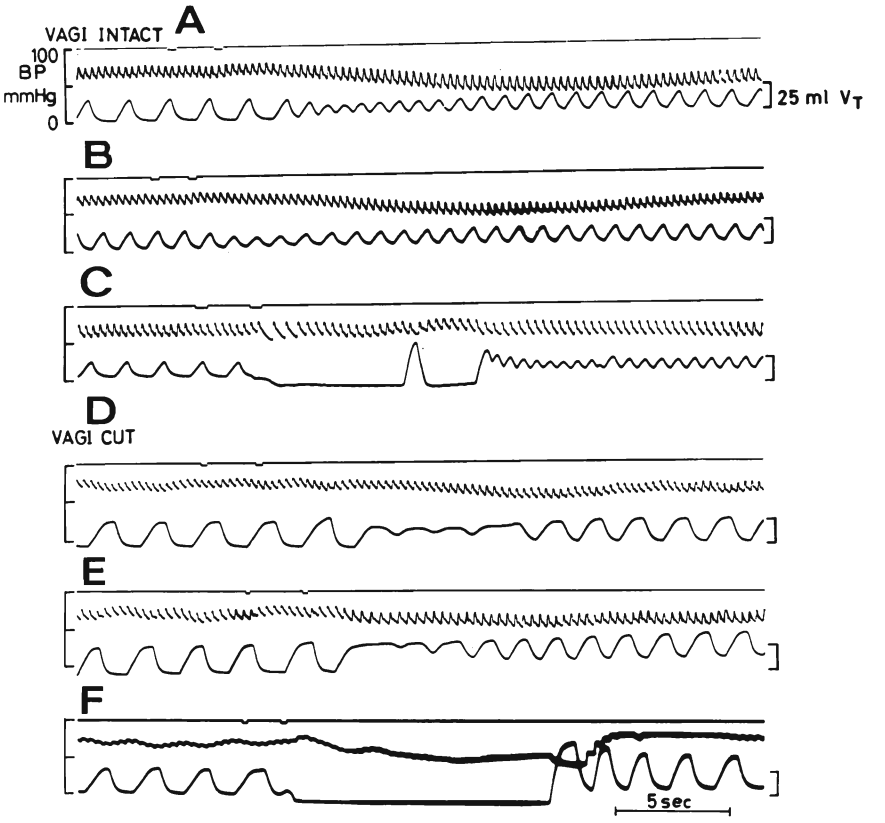

Fig. 5. Blood pressure and tidal volume records and signal marks as in Fig. 3 phenyl diguanide was injected into a femoral vein (*A*, *D*), the left atrium (*B*, *E*) and a vertebral artery (*C*, *F*), before (*A*, *B*, *C*) and after (*D*, *E*, *F*) vagotomy.

It presents the average increases in frequency of breathing in absolute values and as proportional changes.

We conclude from the results: (i) Phenyl diguanide has some action on breathing by stimulation of J-receptors because there is a quantitative difference in responses to injection into the right and left heart (Table I). (ii) After cutting the vagus nerves the breathing frequency response due to phenyl diguanide is still present. The experiments when phenyl diguanide was injected into a vertebral artery indicate that this response probably originates in the brain.

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