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Low activation threshold of juxtapulmonary capillary (J) receptors of the lung

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A B S T R A C T

Respiratory reflexes arising from stimulating juxtapulmonary capillary (J) receptors by increasing doses of phenyl diguanide (PDG) were examined in 18 spontaneously breathing cats. In 60% an immediate and four-fold increase in breathing frequency (fR) was produced by doses as small as 5.1 ± μg/kg (range: 3.5–7.5) thus establishing that a significant increase in fR is produced by J receptors by stimulating them with minimal or threshold doses of PDG. In response to similar minimal doses of PDG J receptor afferent activity increased accompanied by acceleration of breathing rate.

The response to supra threshold doses was either an apnoea followed by rapid shallow breathing (rsb) or to an apnoea preceded by rsb or only to rsb. Respiratory excursions counted from high-speed run records of intrapleural pressure revealed that the apnoeic response obtained in some cases was a phase of high-frequency breathing and not its suspension.

These findings using a chemical stimulus demonstrate that J receptors, with some variability, have a very low threshold for stimulation resulting in notable respiratory acceleration. Thus their afferent output could increase significantly at low intensities of their physiological stimuli such as rise in cardiac output and incipient pulmonary congestion that are generated with mild exercise, to give rise to augmented breathing which is consequently seen.

1. Introduction

Juxta-pulmonary capillary (J) receptors are a group of sensory receptors that lie in the pulmonary interstitium and are innervated by vagal fibres (Paintal,1955). They are accessible *only* via the pulmonary circulation and characteristically are stimulated with latencies as short as 2.0–2.5 sec in response to the chemical phenyl diguanide (PDG) injected intravenously into animals (Paintal, 1969). PDG is a specific stimulant of the J receptors as neither the other well-known lung receptors *i.e.*, the rapidly and slowly adapting pulmonary stretch receptors nor the atrial receptors are stimulated by it (Paintal, 1953). Neural inputs from these receptors increase in response to modest increases in pulmonary blood flow that normally occur during mild exercise (Anand and Paintal, 1980) and to incipient increases in interstitial and pulmonary capillary pressures (Paintal, 1969; Anand and Paintal, 1980; Paintal and Anand, 1992).

The respiratory reflex arising from their relatively weak or gradual stimulation by PDG produces an acceleration of respiration without an initial period of apnoea (Paintal, 1955). This event of weak stimulation of J receptors resulting in a 20–40% increase in ventilation is accompanied by a notable increase in the averaged phrenic nerve activity with consequent fall in end-tidal CO_2 in both normal cats and those with experimental lesions in the brain stem (Anand et al., 1982). Besides tachypnoea or breathing with reduced tidal volume or rapid shallow breathing (rsb), the other reflexes that J receptors give rise to are bradycardia, hypotension and inhibition of exercise in animals (Deshpande and Devanandan, 1970) in healthy individuals (Raj et al., 1995; Anand et al., 2009, 2010; 2012) as well as in cardiac disease patients (Dehghani et al.,2004; Anand et al., 2012, 2014).

However several notable studies have shown that stimulating J receptors also called pulmonary C fibres produce an immediate apnoea by PDG in cats (Schiemann and Schomburg, 1972; Miserocchi, 1978) and by capsaicin in dogs (Coleridge and Coleridge, 1984).

As our correlative studies in human subjects and cats have shown that the mechanism of stimulation and nature of respiratory reflexes elicited by J receptor stimulation are similar in both (Raj et al., 1995) we undertook to clarify these divergent views in cats in the present study. An exigent reason for undertaking this was to establish the level of J receptor stimulation that would increase or reduce breathing frequency in the presence of their natural stimuli in future studies.

The study was carried out in adult cats by recording respiratory frequency in response to injecting a range of PDG doses intravenously. Additional evidence was provided by recording the afferent nerve activity of J receptors in response to similar doses of PDG. All observations were carried out after blocking cardiac receptors by injecting xylocaine into the pericardial sac since our earlier findings had established that respiratory reflex effects including noteworthy durations of apnoea could emerge from stimulation of these receptors by PDG injections (Anand and Paintal, 1980).

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2. Methods

2.1. Animals

Experiments were carried out on eighteen adult cats weighing between 2.5–4.7 kg.

All procedures described below were performed in accordance with Indian National Science Academy's Guidelines for Care and Use of Animals and Scientific Research and were approved by The Institutional Ethics Committee.

2.2. Experimental preparations for recording respiratory and cardiovascular variables and drug delivery

Cats were anaesthetized by injecting 35 mg/kg sodium pentobarbitone (Sagatal, Rhône Merieux Ltd, Wessex, U.K.) intraperitoneally. Supplementary doses of the same anaesthetic were given through a catheter inserted into the right saphenous vein to ensure adequate anaesthesia to prevent spontaneous movements of the animals till the end of the experiment and also delivered when heart rate increased by more than 15%. The tip of the catheter lay in the right atrium (confirmed post mortem); it was also used for injecting PDG into the right atrium (RA). A second catheter was inserted into the right femoral artery and advanced in a retrograde direction such that its tip lay in the thoracic aorta. This was used for recording the blood pressure (BP) *via* a Statham transducer type P23Gb. A thin catheter was also inserted into pericardial sac through an opening between the 4rth and 5th ribs for injecting xylocaine (2%) for blocking sensory receptors and fibres accessible to it as done in an earlier investigation (Anand and Paintal, 1980). The trachea was cannulated and one of its outlets connected to a Palmer "Ideal" respiratory pump for artificially ventilating the cat while opening the chest to insert a malecot catheter for recording intrapleural pressure (IPP). IPP was recorded using a Statham P23 BB transducer. The chest was stitched back and evacuated of air and the cat allowed to breathe spontaneously. The animal's temperature was maintained between 37–38 °C through external heating. At the end of the experiment animals were euthanized with an overdose of sodium pentobarbitone (60 mg i.v.)

2.3. Measurement of respiratory frequency, calculation and presentation of data

Continuous records of IPP and BP were obtained on a Beckman RS Dynograph and on a Racal 7DS tape recorder. The respiratory effects of injecting PDG were studied by recording changes in IPP as expressed in cms H_2O. In general in the cat changes in IPP are equivalent to changes in tidal volume as well as to the integrated phrenic activity and the latter two are a mirror image of the former (see Fig. 1 in both Eldridge 1971 and 1976). IPP is an index of the activity of the respiratory muscles *i.e.*, a fall in IPP indicates an increase in tidal volume and vice versa. Therefore the excursions of IPP were used as a count of respiratory frequency (fR) from its record taken on the dynograph and the value expressed as breaths per min in a given length of time. An increase or decrease in fR (see above) obtained in response to injecting PDG was calculated as a percentage of its control value. Functional mean BP was also calculated from dynograph records taken at a speed of 1 cm/sec.

2.4. Recording neural activity

In two cats impulses from J receptors were recorded from vagal filaments using conventional techniques and set-up using silver-silver chloride electrodes and a Tektronix 122 preamplifier that was at first recorded on a Racal DS7 tape recorder along with the IPP output. Subsequently they were photographed on continuously moving 70 mm Kodak photographic paper. From such records the intensity of receptor discharge was measured by counting the number of impulses that appeared within 2.5 s of injecting PDG. A receptor was identified as J if impulse activity appeared within 2.5 s of injecting phenyl diguanide into the right atrium and if no such response was obtained if injected into the left atrium (Paintal, 1969; Anand and Paintal, 1980).

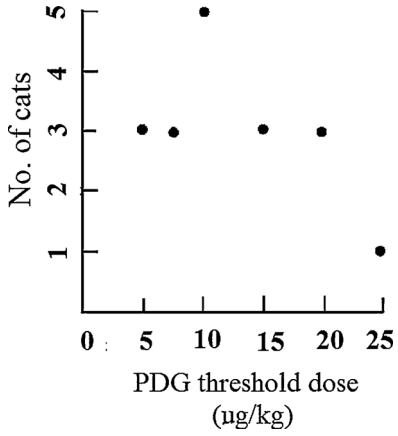

Fig. 1. PDG threshold dose and fR increase.
In a maximal number of cats (n = 11) an increase in breathing frequency (fR) was seen as the first response to injecting threshold doses of PDG as small as 10 µg/kg or less (mean 7.3 ± 0.6 µg/kg; range: 3.0–10.0 µg/kg).

2.5. Drugs

L-phenyl diguanide HCL (Kock-Light Laboratories, Colbbrook, Bucks, UK.) was used in concentrations of 100 µg/ml in saline. The dead space of the catheter was filled with the solution of the drug and appropriate aliquots used to flush it out. Responses to injections of normal saline constituted as control to the above.

Xylocaine as a 2% solution (Astra-IDL Ltd, Bangalore, India) was used for injecting into the pericardial sac.

2.6. Experimental procedure

Protocol 1(a). In all spontaneously breathing cats the response of increasing doses of PDG on IPP was recorded for obtaining its effect on respiratory frequency.

Protocol 1(b). In certain cases a repeat injection of the same dose of PDG was delivered after delivering an injection of 10 mg pentobarbitone i.v. (see Results).

Protocol 2. In two spontaneously breathing cats the impulse activity of J receptors was recorded in response to increasing doses of PDG RA along with their effect on IPP.

2.7. Statistical analysis

Mean values of PDG doses that were injected were expressed as ± SEM. Changes in respiratory frequency were expressed as % age of control values.

P value of threshold doses of PDG for increasing fR and number cats was considered statistically significant if it was < 0.05.

3. Results

3.1. Respiratory reflex response to threshold (least) dose of phenyl diguanide

In all 18 spontaneously breathing cats the first reflex effect that occurred with the least or threshold dose of PDG was an immediate and significant increase in breathing frequency (fR) manifesting itself as rapid shallow breathing. The dose that produced the first perceivable

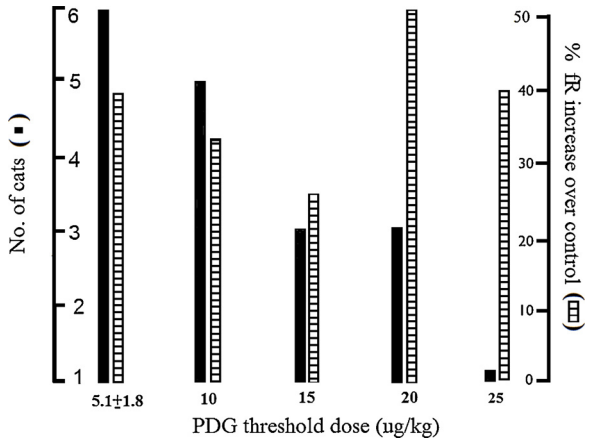

Fig. 2. Percentage increase in fR response to threshold PDG dose.

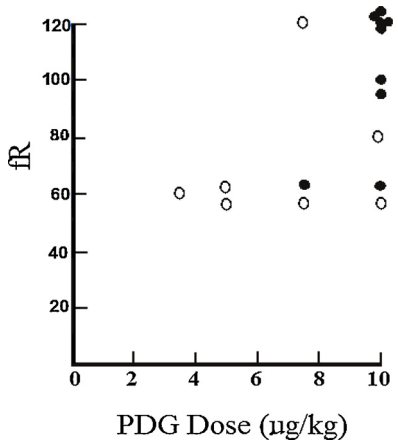

Fig. 3. Response to repeated injections of PDG doses.
In response to repeated injections of PDG injected into the right atrium fR values (breaths/min) seen immediately (O) and after an apnoea (●) show a similarity in the extent of increase in fR amongst these two types of responses to the same dose of PDG.

change in the respiration of a majority of spontaneously breathing cats (61.1%; n = 11) was 10 µg/ kg or less. Of these more than 50% showed an initial increase in fR by 50% over resting respiratory rate with a mean dose as small as 5.1 ± µg/kg; range: 3.5–7.5 µg/kg (Figs.1and 2 ; see also section A of Fig. 4).

In the remaining 39% of cats the least dose that produced the first increase in fR, ranging from 25 to 50% over control values, was 15 µg/kg in 17%, 20 µg/kg in 17% and 25 µg/kg in 5%. The P value of PDG threshold dose (< 10 µg/kg) seen in a majority (61%) of cats was < 0.5.

All injections of PDG produced the well known accompanying fall in BP; an example is seen in Fig. 4.

Saline injected into right atrium did not produce any change in fR.

In a maximal number of cats (n = 11) an increase in breathing frequency (fR) was seen as the first response to injecting threshold doses of PDG as small as 10 µg/kg or less (mean 7.3 ± 0.6 µg/kg; range: 3.0–10.0 µg/kg).

3.2. Extent of respiratory frequency increase over control

The maximal increase in respiratory frequency over control values seen with the smallest or threshold doses used *i.e.*, 3–10 µg /kg was 40% over resting fR. This increase was similar to higher threshold doses and ranged from 30 to 50%.The latency of this increase was similar with all values of threshold doses and these ranged from 2.0 to 2.5 s (Fig. 2).

The figure illustrates the extent of increase in respiratory frequency (% over control) in response to injecting threshold doses of PDG RA. It may be noted that a 40% increase in respiratory rate over control can be produced by doses as small as 5.1 ± 3.5 µg/kg. Higher threshold doses in range *i.e.*,15–25 µg/kg also produced a noteworthy increase in fR which varied from 30 to 53% over control levels.

3.3. Respiratory reflex response to repeat injection of threshold dose

A further observation made in 11% cats (n = 2) was that a second injection of the original threshold dose produced an initial short period of apnoea that was followed by respiratory acceleration which was notably similar in extent to that seen with the first injection. This is shown in Fig. 3 as a comparison of these two events in one of these two cats where 5 µg/kg PDG injected into the right atrium increased fR from 20 to 55 breaths/min (> 150%). A second injection of the same dose at first produced an apnoea that was followed by an acceleration of fR to 60 breaths/min *i.e.*, to a similar extent. A similar effect can be seen in the same figure as being produced by suprathreshold doses of 8 and 10 µg/kg PDG. This then demonstrates that a previous apnoea produced no additional inhibitory effect on the subsequent increase in fR by PDG.

3.4. Respiratory reflex response to suprathreshold doses of phenyl diguanide

On injecting higher than threshold doses of PDG two patterns of respiratory responses were seen with short latencies.

3.4.1. Crescendo type or an immediate increase in fR

In 50% of cats injecting suprathreshold doses of PDG gave rise to rapid, shallow breathing with a latency of 2.5 s which was similar to that seen in response to threshold doses in all cats. One such an example is shown in Fig. 4 where the threshold dose of 5 µg/kg (A) produced a 40% increase in fR with a latency of 2 s and which lasted for 25 s. In response to a suprathreshold dose of 10 µg/kg the fR rate increased by 76% over control within 2.5 s of the injection. The duration of this increase was about 25 s after which the fR came back to the resting control values.

With a yet higher dose of 15 µg/kg PDG (C) the immediate response (latency: 2.5 s) seen was an apnoea or a decrescendo of the existing increased respiratory rate. The breath count during its phase is presented in Fig.5

In response to injecting PDG threshold dose of 5 µg/kg control fR increased by 40% within 2.5 s. (A). With a suprathreshold dose of 10 µg/kg, fR increased in a crescendo manner (B) and with 15 µg/kg PDG an apnoea was produced in response (C). See Fig. 5 for analysis of response in C.

In all those instances where such a crescendo type of response was seen, a repeat injection of the same dose of PDG was delivered after an injection of 10 mg pentobarbitone i.v. This resulted in an apnoea preceding the increase in fR which was subsequently seen. Furthermore the duration of acceleration was notably reduced.

Data of fR taken from Fig. 4C *i.e.*, breath count at rest and on injecting a suprathreshold dose of PDG RA shows that at time zero (control activity) respiratory frequency was 30–35 breaths /min and within 5 s of injecting 15 µg/kg PDG it reached a peak value of 130–150 breaths/min superimposed over what appeared to be a complete cessation of breathing or apnoea.

3.4.2. Decrescendo or apnoeic response

In 25% of the responses to injecting suprathreshold doses of PDG an immediate apnoea was seen as shown in section C of Fig. 4. An analysis of fR *i.e.*, breath count of the same record that can be seen in Fig. 5 shows that on injecting 15 µg/kg PDG the control respiratory frequency of 30 breaths /min reached a peak value of 140 breaths/min within 2.5 s during the phase that was apparent as apnoea or complete

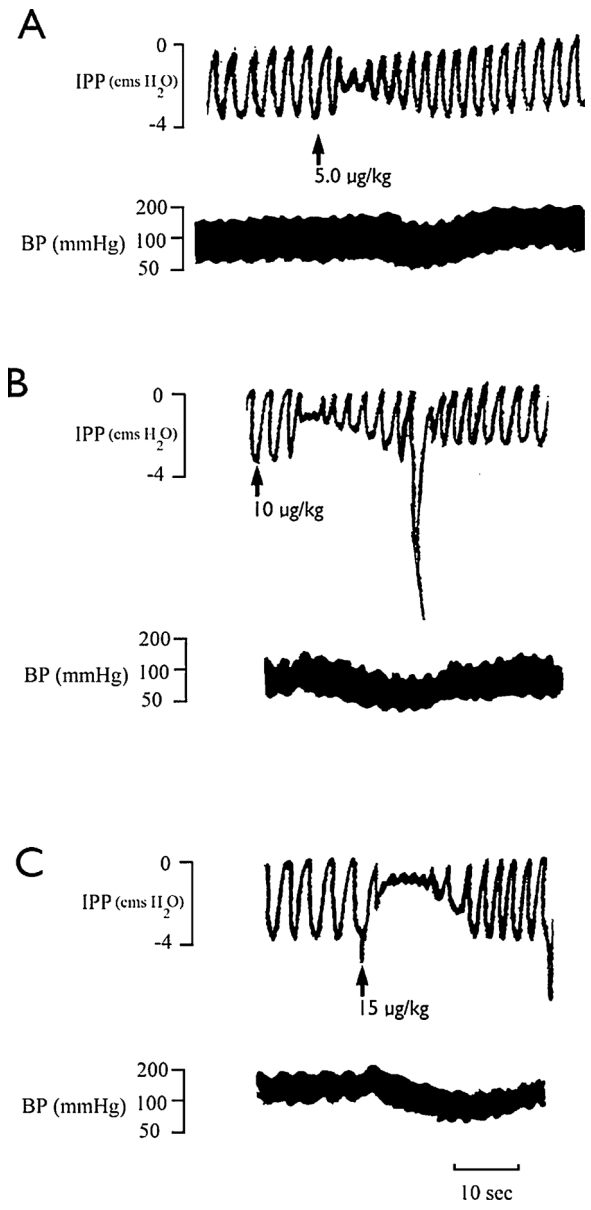

Fig. 4. fR response to suprathreshold doses of PDG (crescendo type).
In response to injecting PDG threshold dose of 5 µg/kg control fR increased by 40% within 2.5 s. (A). With a suprathreshold dose of 10 µg/kg, fR increased in a crescendo manner (B) and with 15 µg/kg PDG an apnoea was produced in response (C). See Fig 5 for analysis of response in C.

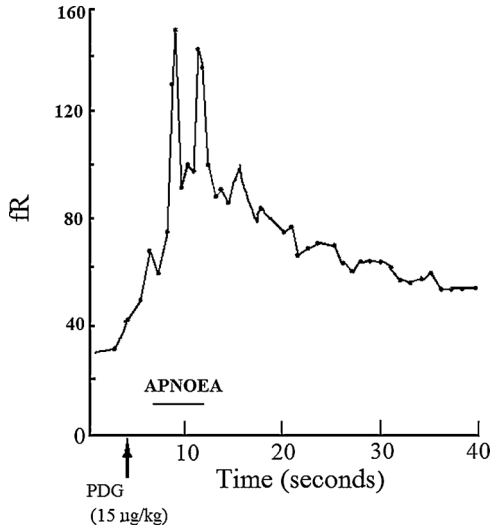

Fig. 5. Analysis of the apnoeic response seen Fig. 4C.
Data of fR taken from Fig 4C *i.e.*, breath count at rest and on injecting a suprathreshold dose of PDG RA shows that at time zero (control activity) respiratory frequency was 30–35 breaths /min and within 5 s of injecting 15µg/kg PDG it reached a peak value of 130–150 breaths/min superimposed over what appeared to be a complete cessation of breathing or apnoea.

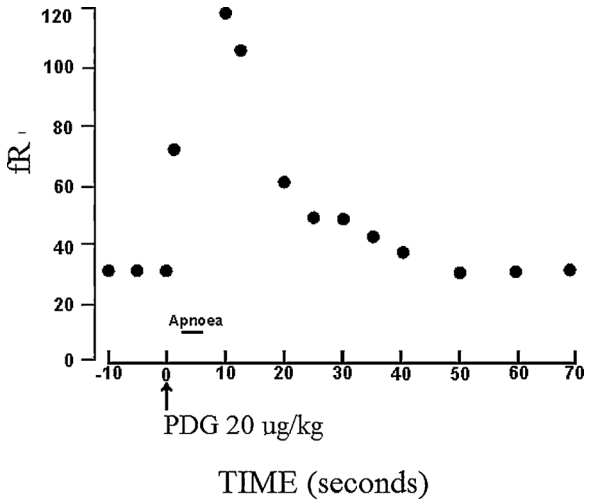

Fig. 6. Analysis of an apnoeic response to suprathreshold PDG dose.
At time zero the control fR of 30 increased to 76 breaths/min within 2.0 s with 20 µg/kg PDG RA. Thereafter fR peaked to 120/min while appearing as an apnoea in the dynograph record. This increase gradually came to control levels over a minute.

cessation of breathing. Another such example is illustrated in Fig. 6 where the breath count plotted against the time lapsed after an injection of 20 µg/kg shows an increase in fR during the phase that appeared as an apnoea in the record.

A variation of the decrescendo response seen in the remaining 25% of cats to injecting suprathreshold doses of PDG was at first a crescendo fR (latency: 2.5 s) followed by a brief decrescendo or apnoea which was then followed by respiratory acceleration.

An example is illustrated in Fig. 7A. The response to injecting 20 µg/kg when recorded at a lower dynograph speed and shown in section A of Fig. 7, appears exclusively to be that of an apnoea. However in section B, which is a fast replay of the same tape-recorded segment but at a faster dynograph speed (see Methods) the phase that appeared to be a complete cessation of breathing in the slow running record was actually a combination of the following: a resting fR of 36 increasing to 76 breaths/min within 2.5 s for 4 s that was followed by a phase of apnea lasting 4 s after which an accelerated rate of breathing re-emerged (63 breaths/min).

A. In response to injecting 20 µg/kg PDG (suprathreshold dose) at arrow an immediate apnoea was seen accompanied by a fall in BP by 30 mm Hg.

B. A fast replay of the same record as in A shows that what appeared only as an apnoea is an immediate (latency: 2.5 s) and brief acceleration of fR followed by an apnoea or decrescendo fR and a reemergence of acceleration of fR

3.5. J receptor responses and respiratory reflex effects evoked by PDG

The impulse activity and duration of stimulation of two single J receptor fibres from two cats recorded in response to injecting threshold and suprathreshold doses of PDG into the right atrium increased

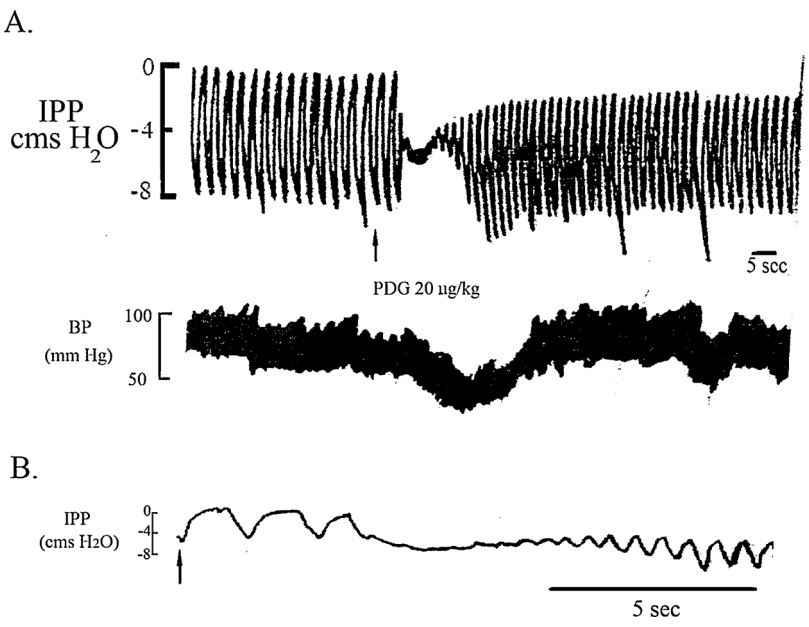

Fig. 7. Crescendo-decrescendo-crescendo response to suprathreshold dose of PDG.
A. In response to injecting 20μg/kg PDG (suprathreshold dose) at arrow an immediate apnoea was seen accompanied by a fall in BP by 30 mm Hg.
B. A fast replay of the same record as in A shows that what appeared only as an apnoea is an immediate (latency: 2.5 s) and brief acceleration of fR followed by an apnoea or decrescendo fR and a reemergence of acceleration of fR.

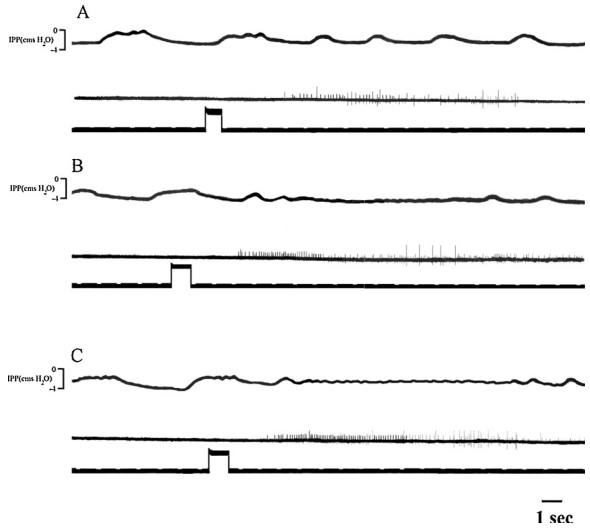

Fig. 8. *J* receptor response and respiratory effects by increasing doses of PDG.
(A) 10μg/kg phenyl diguanide (threshold dose) injected into the right atrium (at signal) stimulated the activity of a hitherto silent *J* receptor to 3 impulses /s after a latency of 2.5 s; fR increased from 12 to 27 breaths/min.
(B) A supra threshold dose of PDG *i.e.*, 15 μg/kg produced a greater stimulation of the receptor to 5.1 impulses /sec and fR increased simultaneously to 24 breaths/sec followed by an apnoea (10 s) and a recurrence of respiratory acceleration to 48 breaths/min.
(C) With 25 μg/kg the neural output increased to 9 impulses/sec and after a brief acceleration of fR to 24 breaths/s an apnoea lasting for 6.5 s occurred; this was followed by a respiratory acceleration to 72 breaths/min.
Traces from top to bottom are of IPP, impulse activity and 1 s time marks with signal for injection.

directly in proportion to the dose injected and the latency of stimulation decreased inversely. In Fig. 8 these responses along with changes in IPP (fR) are shown for one of the cats.

In response to 10 μg/kg PDG (threshold dose) injected into the right atrium the activity of a hitherto silent J receptor increased to 3 impulses/sec after a latency of 2.5 s. Simultaneously with this the respiratory rate increased from 12 to 27 breaths/min and remained rapid for 30 s. A supra threshold dose of 15 μg/kg PDG produced a greater stimulation of the receptor to 5.1 impulses /s that lasted for 10 s and simultaneously with this the respiratory rate at first increased briefly from 12 to 24 breaths/s followed by a 10 s phase of apnoea that was followed by a recurrence of respiratory acceleration to 48 breaths/min. In response to 25 μg/kg PDG (C) the J receptor activity increased to 9 impulses/s after a latency of 1.75 s and fR to 24 breaths/s after which an apnoea appeared lasting for 6.5 s and was followed by a reappearance of respiratory acceleration to 72 breaths/min.

4. Discussion

The principal result from this study done on eighteen, pentobarbitone-anaesthetized cats after blocking cardiac receptors, was that bolus injection of the lowest-possible or threshold dose of PDG produced a four-fold increase in respiratory frequency without an initial apnoea (Figs. 1,2 and 8A). In more than half the cats the dose at which an increase in fR appeared as the first response was less than 10 μg/kg (range 3–10 μg/kg).This established that they have a very low threshold of stimulation and a significant increase in fR is produced by stimulating them minimally. Thus it is not surprising that an increase in fR as *the* first response arising from chemically stimulating the J receptors has so far been missed in several noteworthy studies that used doses as high as 100–150 μg s (Schiemann and Schomburg,1972) and 150 μg s (Miserocchi, 1978) giving rise to the view that their stimulation reduces respiratory frequency. Nevertheless, large doses of PDG have been reported to produce respiratory acceleration if injected slowly (Paintal, 1955; Anand and Paintal, 1980).

An apnoea resulting in response to a large and rapidly delivered dose of phenyl diguanide would be produced by a sudden peak in J receptor afferent inputs flooding the respiratory control areas whereas when it receives fewer impulses with smaller and slowly-delivered doses an acceleration of breathing results. Furthermore, since rapid breathing above a certain rate must occur at the expense of depth, rapid becomes shallow (Paintal, 1955).

In the present study supportive data was provided by recording J receptor responses and changes in breathing rate in response to increasing doses of PDG. Thus a small dose of PDG (10 μg/kg) not only produced a noteworthy stimulation of a silent and singly identifiable J receptor but also an increase in fR from 12 to 27 breaths/min. Higher doses intensified the receptor's afferent output and gave rise to an apnoea preceded and followed by an increase in fR.

4.1. Contribution of respiratory reflexes from other receptors

The presence of xylocaine in the pericardial sac allowed the reflex respiratory effects to be examined exclusively from J receptors *i.e.*, in the absence of similar contributions from cardiac receptors and in the absence of bradycardia (Anand and Paintal, 1980). An influence by bronchial receptors on the observed responses was also ruled out as in cats they neither influence respiration nor blood pressure while being stimulated significantly by PDG and capsaicin injected into the bronchial circulation (Anand, 2000).

4.2. Response to suprathreshold doses and veracity of apnoeic response

A further analysis of the present results shows that not all observed apnoeas are cessation of inspiratory and expiratory activity but phases of accelerated breathing. A close examination of the record in Fig.7 yielded evidence that what appeared as an apnoea was actually a phase of high-frequency breathing and not its suspension.

Furthermore a comparison of the *extent* of increase in fR, as seen in Fig.3,which is either immediate or after an apnoea, shows a similarity between the two. This was also seen when the second injection of PDG, after the first having given rise to an apnoea, produced the same increase in fR (as it did in the absence of apnoea).This showed that a previous apnoea produced no additional inhibitory effect on the subsequent increase in fR by PDG. This view garners support from a study on rats that suggests that apnoea and accelerated breathing are features of a common pathway (Zhang et al., 2012). The study showed that rapid shallow breathing produced by activating the conglomerate of bronchopulmonary afferents by phenyl biguanide (an additional name of phenyl diguanide) could be switched to an apnoea by injecting fentanyl- an opioid into the nodose ganglion in which the cell bodies of these vagal afferents lie. In the present study under different conditions of anaesthesia higher doses of PDG produced either an apnoea or an increase in fR. This also confirmed observations of earlier study where the degree of inhibition of phrenic discharge in response to PDG showed that an apnoea was produced with higher doses of PDG *only* under conditions of deeper levels of pentobarbitone anaesthesia (Anand and Paintal,1980).

The crescendo-decrescendo patterns of breathing that were produced by suprathreshold doses of PDG are essentially phases of tachypnoea following apnoea (and *vice versa*) and are the mechanism that maintains regular ventilation in the presence of changing arterial gas tensions brought about by these two events (Haldane and Priestly,1905; Mitchell et al., 1966).

4.3. Significance J receptor stimulation at physiological levels

As seen in Fig. 8, J receptors are normally inactive (Paintal, 1955). In the present study in a majority of cats respiratory acceleration occurred with a minimal or threshold dose of PDG *i.e.*, 10 μg/kg or less. This dose yields an average frequency of 0.7 impulses/s by doubling cardiac output (Anand and Paintal, 1980). From these collective observations it may be inferred that the minimal doses of PDG that produce respiratory acceleration are equivalent to the stimulation of J receptors by a 133% rise in pulmonary blood flow or when cardiac output is approximately doubled (Anand and Paintal, 1980). An increase in cardiac output which is known to occur even with modest exercise (Åstrand et al., 1964) would stimulate J receptors giving rise to respiratory acceleration, dyspnoeic sensations, reflex bradycardia (Paintal,1955) and inhibition of muscles leading to termination of exercise (Deshpande and Devanandan, 1970; Anand et al., 2010). The reflexes of exercise termination and bradycardia constitute a protective mechanism that reduces pulmonary blood flow and pulmonary capillary pressure so as to prevent pulmonary interstitial congestion from occurring. Although no direct evidence is available as yet, however it can be speculated that J receptors afferents represent a sensory mechanism that ensures that the volume of the extravascular water remains minimal which according to Miserocchi (2009) would guarantee a minimal thickness of the air-blood barrier. It may also be relevant to investigate if J receptors have a role to play in limiting alveolar fluid extravasation under edemagenic conditions by reflexly diverting blood flow to the lung corner vessels by active precapillary vasoconstriction –a mechanism that is suggested by the recent findings of Mazzuca et al. (2019).

4.4. Intense stimulation of J receptors

The average frequency of J receptor discharge seen by stimulating them with suprathreshold doses of PDG in cats in the range 25–40 μg/kg, is 5–7 impulses/s (7.5 ± 6.3 SEM). This level of activity amounted to intense stimulation of J receptors and was reported in cats during pulmonary congestion produced by injection of alloxan or by the occlusion of the aorta and was associated with a marked rise in PAP and occurrence of pulmonary oedema (Paintal, 1969). The relationship between the respiratory symptoms and exercise-limitation by increased J receptor output in pulmonary congestion and raised PAP has been established in patients with mitral stenosis (Anand et al., 2009) and in those with congenital heart disease (Anand et al., 2014).

In healthy subjects under severe physiological conditions such as during marathon running (Zavorsky et al., 2014) and trekking at high altitude (4240–5160 mt s), a mild to moderate interstitial lung oedema was seen but without any discernible signs of subclinical lung oedema (Lim et al., 2019). The absence of lung oedema in these individuals best can be explained by the experimental findings, in rabbits, of Miserocchi et al. (1993) that showed that an increase in pulmonary interstitial pressure could occur much before the actual appearance of oedema fluid in the interstitium; perhaps being a mechanism that prevents an early pulmonary alveolar flooding from occurring. In terms of the role of J receptors under these severe physiological conditions it would be invaluable to know the accompanying status of the respiratory parameters and exercise capability of these individuals.

Teleologically, the appearance of apnoea at higher J receptor inputs that would occur at high levels of exercise would reflexively lead to a reduction in cardiac output and hence termination of exercise. Reducing the increase in cardiac output would cause a reduction of pulmonary blood flow and thereby of pulmonary capillary pressure. Thus the reflexes from J receptors at intense levels of exercise too, ensure a protective mechanism against rupture of some pulmonary capillaries which could lead to haemoptysis and which indeed has been reported in extreme cases such as in marathon runners (McKechnie et al., 1979) and racing thorough bred horses (West and Mathieu-Costello, 1995). The influence of J receptor-induced apnoea on cardiac output could be investigated further since it's known that sleep-induced apnoea does decrease cardiac output and stroke volume in human subjects (Garpestad et al., 1985).

In conclusion the study resolved that, with some variability, the J receptors have a very low threshold of stimulation and produce significant increase in fR when stimulated minimally by threshold doses of PDG. Thus their afferent output could increase significantly at low intensities of their physiological stimuli such as incipient pulmonary congestion, which is generated with mild exercise, to give rise to augmented breathing which is consequently seen. An apnoea when seen in response to injecting large doses of any specific chemical substance is a manifestation of the rate of its injection and the state of ánaesthesia of the animal.

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Conflict of interest

No conflict of interest from any source; the funding agency is Governmental support for basic and applied research.

A.S. Paintal contributed to some analysis of results and Figs. 1,3 and 7 were drawn by him. All animal experimental work, calculation of results, remaining analysis of data and writing up of the manuscript has been contributed by me.

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Late Dr A.S.Paintal and I jointly conceived the idea of investigating the issue of disparate views about the role of J receptors in influencing respiration under physiological and especially under pathological circumstances.

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