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MECHANISMS UNDERLYING ENHANCED RESPONSES OF J RECEPTORS OF CATS TO EXCITANTS IN PULMONARY OEDEMA

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SUMMARY

1. The responses of J receptors to certain excitants were recorded during pulmonary oedema produced by phosgene gas (320–1080 p.p.m.) or alloxan, 150 mg kg^{-1} I.V., in cats anaesthetized with sodium pentobarbitone, 35 mg kg^{-1} I.P.

2. The responses of fourteen (out of fifteen) J receptors to phenyl diguanide (PDG) were greatly enhanced after phosgene, the enhancement being highly significant ($P = < 0{\cdot}01$) in twenty-one out of twenty-six responses. The enhancements were also highly significant after alloxan in the case of another twelve receptors. Similar enhancements were observed in the case of responses to nicotine and capsaicin. This suggests that the enhancement of the responses of J receptors to excitants occurs in a non-specific manner after phosgene and alloxan.

3. The enhanced responses occurred in the absence of any significant increase in the estimated concentration of the excitants in pulmonary artery blood.

4. The enhanced responses to PDG were not closely related to the oedema-induced activity; several occurred during periods of silence of the receptors and in thirteen receptors the enhanced responses occurred before the increase in the oedema-induced activity had begun.

5. A possible role of histamine, 5-HT, prostaglandins and bradykinin in enhancing the responses to PDG after phosgene was excluded.

6. The results therefore suggest that the non-specific enhancement of the responses of the J receptors to excitants must be due to the increased permeability of the capillaries produced by phosgene and alloxan leading to greater movement of the excitants to the J receptors. However, certain unidentified factors may also be involved.

INTRODUCTION

Interstitial pulmonary oedema is produced by procedures that raise pulmonary capillary pressure (see Staub, 1974). It is also produced by increasing the permeability of the pulmonary capillaries following injection of alloxan (Staub, Nagano & Pearce, 1967; Goetzman & Visscher, 1969) or by ventilating the lungs with phosgene (Kennedy *et al.* 1989) or chlorine gas (Goodman & Gilman, 1955). All three agents cause marked stimulation of the J receptors (Paintal, 1969; Coleridge & Coleridge, 1977; Anand, Paintal & Whitteridge, 1986) with simultaneous

production of interstitial oedema followed by frank outpouring of oedemal fluid (e.g. see Paintal, 1969; Coleridge & Coleridge, 1977).

Hitherto it has been assumed that the excitation of the receptors under such conditions is due to increase in interstitial volume *per se* (Paintal, 1969; Roberts, Bhattacharya, Schulz, Coleridge & Coleridge, 1986). However, such a conclusion, although apparently reasonable, can be truly valid only if the role of certain endogenously produced excitatory substances such as 5-HT (Paintal, 1955), histamine (Paintal, 1974; Paintal & Anand, 1984), prostaglandins (Coleridge, Coleridge, Ginzel, Baker, Banzett & Morrison, 1976) and bradykinin (Kaufman, Coleridge, Coleridge & Baker, 1980) are excluded. This is particularly relevant in the case of excitation of the receptors after administration of agents that produce pulmonary oedema by injuring the capillaries, i.e. chlorine, alloxan and phosgene. In connection with this an important question that needs to be answered is, will these excitants have a greater excitatory effect during pulmonary oedema produced by increasing the permeability of the capillaries? An attempt has been made to answer this question in the present study by observing the effects of three excitants of J receptors, namely phenyl diguanide (PDG), nicotine and capsaicin before and during pulmonary oedema produced by administration of phosgene and alloxan.

METHODS

Experiments were carried out on cats anaesthetized with 35 mg kg^{-1} sodium pentobarbitone (Sagatal, May & Baker Ltd, Dagenham, UK) given intraperitoneally; a few were anaesthetized with chloralose (75 mg kg^{-1}, I.V.) after induction with trichlorethylene. Since the methods and experimental details used in the present investigation have been described in detail in a recent paper (Paintal & Anand, 1992), only a short description of these will be given. Briefly, catheters were positioned with tips in the right atrium, left atrium, aorta and pulmonary artery and were connected to Statham-type pressure transducers for recording intravascular pressures. The cats were artifically ventilated with a Palmer 'Ideal' respiratory pump set to run at 17 cycles min^{-1}. The intratracheal pressure was recorded with a Statham-type PM5 transducer and since the tidal volume was kept constant, changes in compliance could be easily estimated from values of peak intratracheal pressure. The end-tidal CO_2 percentage was approximately 3·5–4 % and it was monitored with an LB 2 Beckman CO_2 analyser.

The cardiac output was measured using the thermodilution technique. The concentration of injected drugs was estimated using the technique described in detail earlier (Paintal & Anand, 1992) in order to obtain a measure of peak concentration, mean concentration over the first three seconds ($[X]_{0-3s}$) and the concentration–time area ($\mu g\ ml^{-1}\ s$) to 50 % peak concentration. This provides a measure of the mean concentration over that period multiplied by the time (see Methods and Fig. 5 in Paintal & Anand, 1992).

Pulmonary capillary pressure (PCP)

The PCP was estimated using the following formula used by Snashall, Weidner & Staub (1977):

$$PCP = P_{la} + 0{\cdot}4\ (P_{pa} - P_{la}),$$

where PCP is the pulmonary capillary pressure, and P_{pa} and P_{la} are the pressures in the pulmonary artery and the left atrium respectively.

Preparation and administration of phosgene gas

Phosgene gas was obtained by warming 2–5 ml of toluene–phosgene mixture (Fluka) and collecting it in a steel tank of 77 l capacity. The resulting phosgene–air mixture contained 320–1080 p.p.m. phosgene in different experiments. The mixture was administered through the respiratory pump. The concentration of phosgene was measured with a 3061 Autospot analyser (Seiger Ltd, Dorset) after further dilution with air.

Recording set-up and identification of J receptors

Fibres from J receptors were dissected off the vagus nerve in the neck and impulses recorded from them using an Isleworth type 102 or Tektronix type 122 preamplifier. The J receptors were identified using known criteria (see Paintal & Anand, 1992).

Experimental procedure

After identifying a J receptor, its responses to a fixed dose of PDG (usually about 12–18 $\mu g\ kg^{-1}$) were recorded following two to eight (usually three to four) injections of PDG at intervals of approximately 4 min between injections. The doses chosen were clearly suprathreshold for the receptors, usually 12–18 $\mu g\ kg^{-1}$, such that they yielded a response after every injection of PDG. These responses before administration of phosgene were called control responses and their mean values and S.D.S. are shown in Fig. 2 (abscissa). The same procedure was followed in the case of injections of nicotine (usually 18 $\mu g\ kg^{-1}$) or capsaicin (usually 2–3 $\mu g\ kg^{-1}$) but in some cases only one control injection was given. The responses were recorded on a Racal 7 DS tape-recorder along with the various intravascular pressures, intratracheal pressure, cardiac output and [PDG]. The control responses were recorded both before and after injecting pheniramine maleate (1 $mg\ kg^{-1}$) and acetylsalicylic acid (10 $mg\ kg^{-1}$) in eleven cats. These drugs, which respectively blocked the effects of histamine and prevented effects by prostaglandins, were not injected into three cats. Thereafter the phosgene–air mixture was administered through the respiratory pump until the typical increase in discharge due to interstitial oedema set in. The responses to PDG were recorded as before at suitable intervals (> 5 min) between injections. The records continued for as little as 10 min or as long as 70 min after phosgene administration was begun (depending on the viability of the vagal filament on the recording electrodes or state of the cat). Finally, photographic records were made from taped records using a camera with continuously moving 70 mm photographic paper and a Tektronix type 7704 A oscilloscope. In addition a Beckman-type RS dynograph was used for recording the left atrial pressure and the pulmonary artery pressure during the experiment.

The procedure described above was also adopted in the case of experiments with alloxan instead of phosgene except that no injections of pheniramine maleate or acetylsalicylic acid were given to the cats.

Assessment of pulmonary oedema

The occurrence of pulmonary oedema after phosgene or alloxan was inferred from the appearance of frothy oedemal fluid in twenty out of twenty-two cats. In half of these cats oedemal fluid appeared in the tracheal cannula while impulses were still being recorded. In the remaining half it appeared from the cut surfaces of the lungs on application of gentle pressure soon after the recording of impulses was over. It is presumed that such oedemal fluid would also have appeared in the remaining two cats had the experiment continued for more than 1 h after the administration of phosgene.

Analysis of results and statistical analysis

The latency of the response to PDG (or other excitant) was measured from the moment the concentration of PDG suddenly rose in the blood of the pulmonary artery to the first impulse of the resulting train of impulses. The maximum number of impulses over 1 s in this train was measured and this was called the maximum intensity of discharge and expressed as impulses s^{-1}. The total number of impulses in the train (i.e. until the frequency dropped to a low level of approximately 1 s^{-1}) was also counted. This total count constituted the main measure of the intensity of the responses of the receptors to PDG or other excitants.

The means and S.D.S of the maximum intensity of discharge and the total number of impulses produced by PDG (or other excitant) in the control injections were determined. The means and S.D.S of the responses after phosgene or alloxan, although calculated, were not included in the data presented as the responses to PDG after phosgene increased with time (e.g. see Fig. 3) and one could not observe a steady state in the responses of most of the receptors after phosgene. However, since the maximum responses after phosgene tended to occur about 20–40 min after start of phosgene administration, the measurements during this interval after phosgene have been selected for inter-receptor comparisons except in the case of three receptors; in these three the only records available were 10 min after phosgene. All such responses, sometimes two or three

in certain receptors (mean values taken in such cases), have been included in the data presented in Fig. 2, which consist of responses from fifteen receptors.

The significance of the difference from control of each one of the responses after phosgene or alloxan was established at the 1 or 5 % level if it exceeded the upper limit of the control value by 3·2 × S.D. or 2 × S.D. respectively.

Drugs

The drugs used were PDG, white crystalline powder of 1 phenyldiguanide HCl (Koch-Light Laboratories Ltd, Bucks), 100 μg ml^{-1}; nicotine (Sigma Chemical Co., USA), 100 μg ml^{-1}; 5-HT (Sigma Chemical Co., USA), 100 μg ml^{-1}; capsaicin (Sigma Chemical Co., USA), 10 or 25 μg ml^{-1}; bradykinin (Sigma Chemical Co., USA), 10 μg ml^{-1}; histamine acid phosphate (Span diagnostic (P) Ltd, Surat, India), 100 μg ml^{-1}; pheniramine maleate (Avil injections, Hoechest, Bombay, India), 1 mg ml^{-1} dissolved along with sodium bicarbonate as described by Palmer, Piper & Vane (1973); metoclopramide (Beecham Pharmaceuticals, Surrey), 1 mg ml^{-1}.

RESULTS

Effect of phosgene on responses of J receptors to PDG

The responses of fifteen J receptors to PDG under control conditions were compared with the responses of the same receptors after administration of phosgene to the same dose of PDG. Figure 1 provides an example of the responses obtained. It shows clearly that the response of this receptor to PDG was greatly enhanced 36 min after phosgene. The latency for stimulation also fell significantly ($P < 0{\cdot}02$), in this case. Figure 1*B* also shows that this enhancement occurred without any increase in the mean concentration of PDG. Such responses were recorded following most of the twenty-six injections of PDG after phosgene in fifteen receptors as shown in Fig. 2, which also indicates that the enhancement after some of the injections was not as great as that shown in Fig. 1. However, most of the responses were significantly greater than the control values at the 1 or 5 % level of significance. In fact Fig. 2, which gives the standard deviation of the control values before phosgene, shows that the total number of impulses produced by PDG (Fig. 2*B*) after phosgene were significantly greater at the 1 % level in twelve receptors and at the 5 % level in two. In only one receptor the responses to PDG were actually the same or less than the control responses. This receptor was exceptional in that it had an unusually high activity of about 2 impulses s^{-1} to start with which did not increase significantly after phosgene. Qualitatively similar increases in the maximum intensity of discharge were seen after phosgene (Fig. 2*A*).

In most receptors the enhanced responses to PDG usually set in within about 6 min after starting ventilation with phosgene. In four receptors there was clearly no increase between 2 and 10 min after phosgene. The responses to PDG increased gradually (e.g. Figs 3 and 4*B*) in different receptors at different times. Therefore, for making valid inter-receptor comparisons the procedure described in Methods was adopted.

Role of [PDG] and PCP

Reliable records of estimated [PDG] were available in the case of eight receptors. In these it was established that the increased responses to PDG after phosgene were not due to increased [PDG] because $[PDG]_{0-3s}$ (or the concentration–time area to

50 % peak concentration) was either the same (Figs 1 and 3), less than control or not significantly above control value ($P < 0{\cdot}05$). Neither could they be attributed to possible increases in PCP because the mean PCP after phosgene, which was 12·8 mmHg, was lower than the control PCP (14·1 mmHg) in eight cats. However, as shown already PCP plays little or no role in this (Paintal & Anand, 1992).

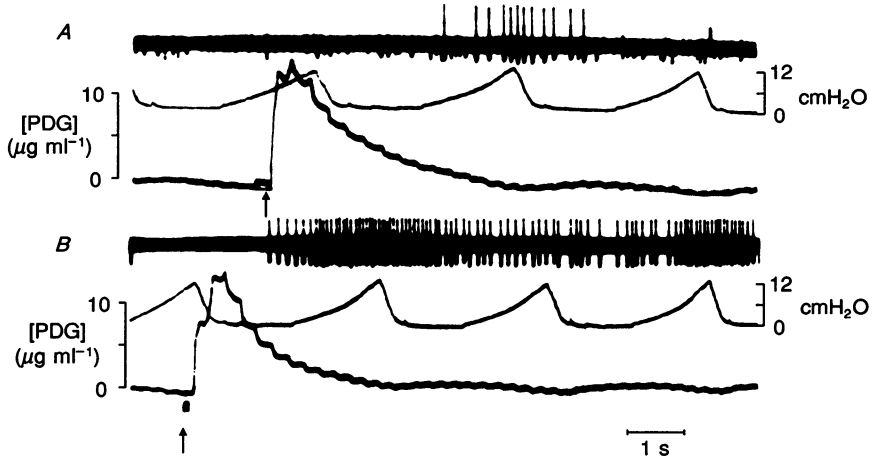

Fig. 1. Responses of a J receptor to injections of 12 μg kg^{-1} PDG at signals (arrows) before phosgene (*A*) and 36 min after phosgene (*B*). The mean concentration of PDG (i.e. $[PDG]_{0-3s}$) was 5·0 μg ml^{-1} in both *A* and *B*. The cardiac output was also about the same in both. Only part of the response in *B* is shown. Note, hardly any rise in intratracheal pressure (middle traces); the lowest trace in each record is of PDG concentration.

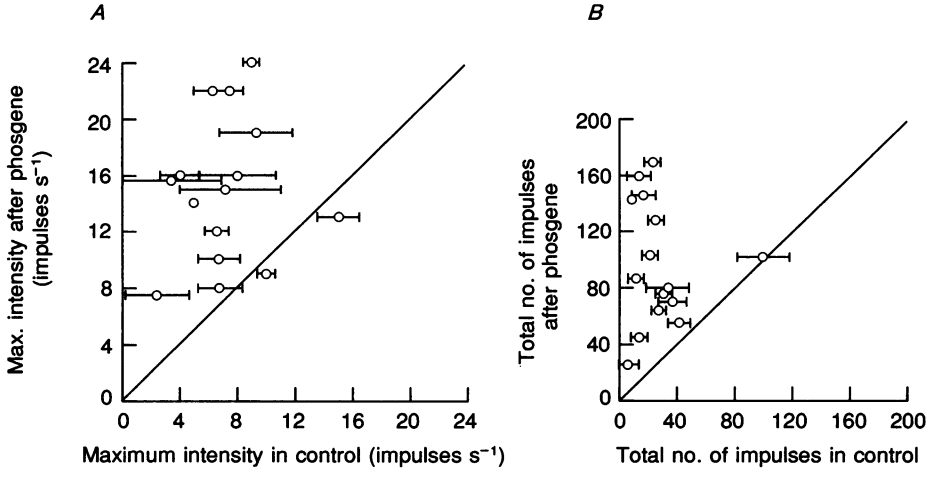

Fig. 2. Comparison of the mean responses of fifteen J receptors to PDG under control conditions (bars are ± 1 S.D.) with those obtained after phosgene using the same dose (ordinate). *A*, maximum intensity of discharge; *B*, total number of impulses.

Does phosgene act as a PDG receptor agonist?

It is possible that phosgene might potentiate the excitatory effect of PDG on the J receptors by acting as an agonist on the same membrane receptors as those on which PDG acts. Such a possibility is unlikely because had it acted in this way then one would have expected such an action to have set in within a few seconds and not taken several minutes to act. However, in order to test this possibility we recorded

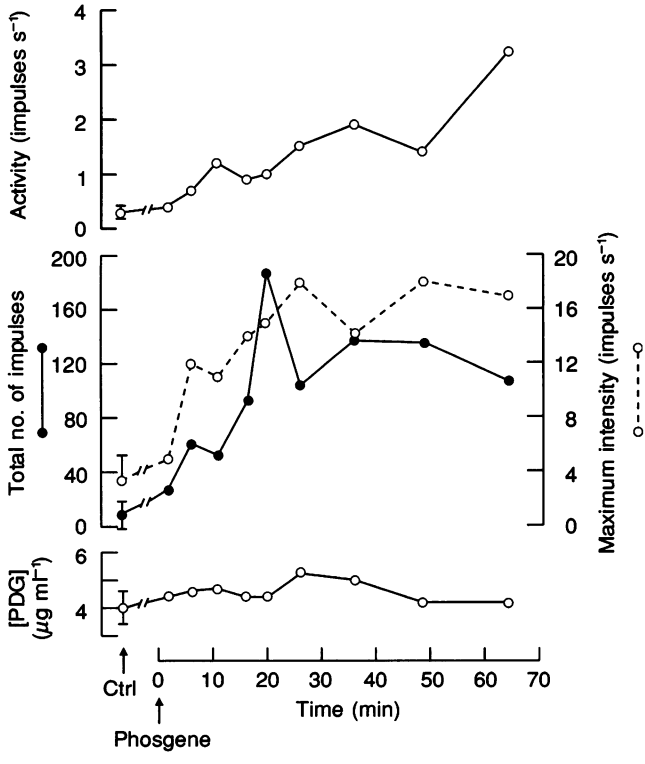

Fig. 3. Responses of a J receptor to control injections of 12 μg kg^{-1} PDG before and nine injections of the same dose of PDG at various times after phosgene. The oedema-induced activity in the receptor (uppermost curve) was measured before injecting PDG each time. Bars on the various control values before phosgene represent ± 1 S.D. Note only small variations in $[PDG]_{0-3s}$, most of them being insignificant compared to control values.

the effects of PDG before and after injecting metoclopramide, an antagonist of 5-HT and PDG (Fortune, Ireland & Tyers, 1983; Ravi & Dev, 1988), on three receptors. In all three the excitatory effect of PDG was abolished after prior injection of 1 mg kg^{-1} metoclopramide without affecting in any way the oedema-induced activity produced by phosgene itself. These observations show that PDG and phosgene excite the receptors through different mechanisms respectively and that phosgene does not potentiate the excitatory effect of PDG directly.

Effect of histamine, 5-HT and bradykinin

In the case of five receptors injections of histamine (18–50 μg kg^{-1}) 40–90 s before injecting PDG enhanced the responses to PDG; significant enhancement occurred

in three of them. This potentiating effect of histamine was blocked for over 30 min after injecting pheniramine maleate (1 mg kg^{-1}) in all the five receptors.

Injecting PDG about 40 s–3 min after a prior injection of 5-HT (10–20 $\mu g\ kg^{-1}$) caused either no change or it reduced the responses of eight receptors to PDG; in three the reduction was significant ($P < 0{\cdot}05$). Similarly prior injections of

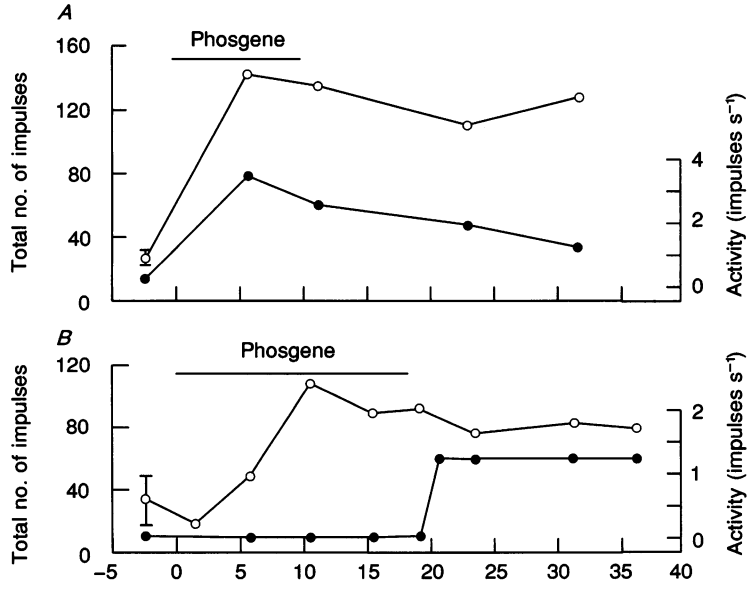

Fig. 4. Responses of two J receptors (*A* and *B*) showing lack of correlation between the level of oedema-induced activity (●) and the total number of impulses (○) produced by serial injections of PDG 18 $\mu g\ kg^{-1}$. Control mean values ± S.D. are shown before phosgene. Phosgene was turned on at zero time and was given for 10 min in *A* and 18 min in *B*.

bradykinin (1 $\mu g\ kg^{-1}$) (which itself did not stimulate the receptors) did not enhance the responses of four receptors to PDG. In fact in two the responses to PDG were reduced for 4–8 min after injecting bradykinin.

From these results it appears that the enhancement of the responses to PDG after phosgene are unlikely to be due to an action by any of the above mediators.

Relationship of oedema-induced activity to magnitude of responses to PDG

The time of onset of oedema-induced activity after phosgene varied widely in different receptors (e.g. Fig. 4), being as short as 25 s in one receptor and as long as 20 min in another; usually the time of onset was between 4 and 19 min after phosgene. However, the responses to PDG were unrelated to the activity, either to the time of onset of this activity or to the intensity of this activity. In fact the maximum intensity of discharge or the total number of impulses produced by PDG bore no relationship to the intensity of the oedema-induced activity present at the time of injecting PDG (Figs 3 and 4). It is noteworthy that the maximum responses to PDG in most receptors occurred several minutes before the receptors had attained their maximal level of oedema-induced activity. This is clearly shown in Figs 3 and 4*B*; similar behaviour was seen in twelve other receptors. Moreover, in

certain receptors the maximum responses to PDG continued to occur even though the level of oedema-induced activity, after reaching a peak, fell to a lower level (Fig. 4*A*) or the receptor had even become silent. Furthermore, in the case of receptors which had the typical intermittent activity after phosgene, enhanced

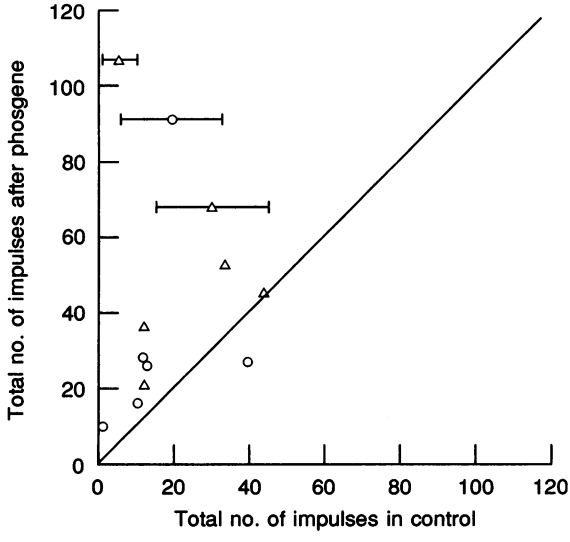

Fig. 5. Comparison of the mean responses of six J receptors to nicotine (○) and capsaicin (△) under control conditions before phosgene (bars are ± 1 S.D.) with those obtained after phosgene using the same dose of the excitant (ordinate).

responses to PDG were observed during the silent periods, i.e. during absence of oedema-induced activity (e.g. Fig. 1*B*). In four receptors the activity that appeared after phosgene was linked to the respiratory cycle. The effect of such respiration-linked activity on the responses to PDG was recorded following eight injections of PDG. No enhancement of the responses to PDG by the oedema-induced activity was observed following any of the eight injections of PDG.

Relationship to intratracheal pressure

The intratracheal pressure rose gradually after phosgene resulting in a fall in compliance which amounted to 24 % of control in twelve cats (range, 0–35 %). The degree of fall bore no relationship to the degree of enhancement of the responses to PDG. For example, in the case of the receptor of Fig. 3 the compliance had fallen by only 7 % 1 h after the start of phosgene administration. These results indicate that the enhanced responses were not related to total fluid accumulation in the lungs on which the fall in compliance depended.

Responses to nicotine and capsaicin

The responses of five out of six J receptors to nicotine and capsaicin were significantly enhanced after phosgene (Fig. 5). In the case of one receptor in which

the responses to both drugs were lower or unchanged after phosgene, the responses to PDG were similarly lower than control. In Fig. 6 the percentage increases in the responses of the receptors to nicotine and capsaicin after phosgene (ordinate) are compared with the percentage increase in the response of the same receptors to

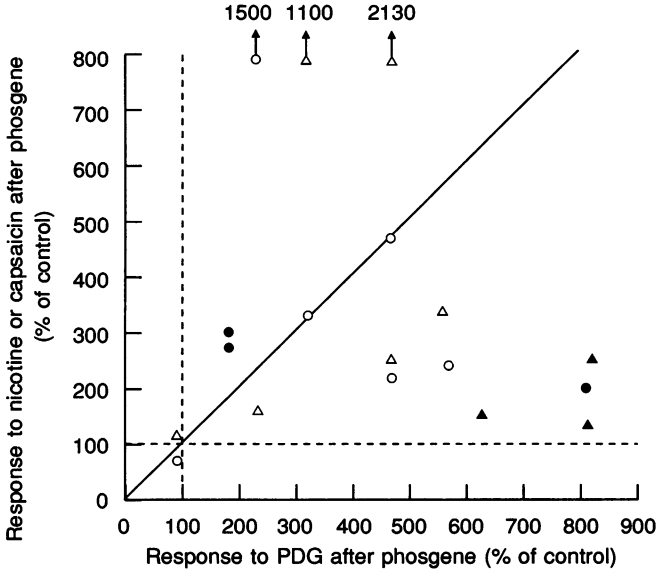

Fig. 6. Comparison of post-phosgene responses of J receptors to PDG (abscissa) with the post-phosgene responses of the same receptors to nicotine (○) and capsaicin (△) (ordinate). The data relate to the total number of impulses produced by each injection of the three excitants and is expressed as percentage of control responses before phosgene, e.g. data for PDG on abscissa is : Total no. of impulses by PDG after phosgene/Total no. of impulses by PDG (Control) × 100. The filled symbols relate to the corresponding responses before and after alloxan. The dashed lines denote control.

PDG after phosgene (abscissa). Identical percentage changes were obtained in the case of nicotine involving three receptors; these are shown on the line of identity. In the case of the other receptors the responses to nicotine and capsaicin relative to those of PDG were variable, but in general one could conclude from Fig. 6 that the responses to nictoine and capsaicin after phosgene increased qualitatively in the same way as in the case of PDG.

Effect of alloxan on responses to PDG nicotine and capsaicin

The responses of twelve J receptors to PDG were recorded before and after injecting alloxan intravenously (150 mg kg^{-1}). The responses of all of them increased markedly after alloxan, the increase being highly significant ($P < 0{\cdot}01$) (Fig. 7). Records of [PDG] were available in the case of six receptors of five cats. In four of them it was established that the enhanced responses to PDG after alloxan occurred in the absence of any significant increase in the mean concentration of PDG ($[PDG]_{0-3\,s}$ or concentration–time area to 50 % peak concentration). In the

case of the remaining two receptors (with fibres in the same filament) a possible contribution by increased [PDG] to the enhancement of the responses to PDG could not be ruled out. Thus it can be concluded that the enhancement of the responses to PDG after alloxan were qualitiatively similar to those after phosgene.

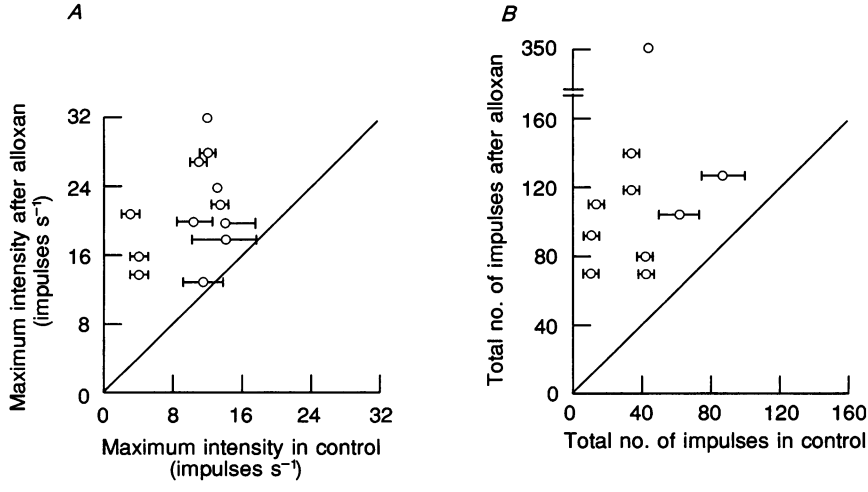

Fig. 7. Comparison of the mean responses of twelve J receptors to PDG under control conditions before alloxan (bars are ± 1 S.D.) with those obtained after injecting alloxan using the same dose of PDG (ordinate). *A*, maximum intensity of discharge; *B*, total number of impulses in ten receptors; in two receptors the total could not be counted reliably owing to admixture with impulses from other fibres in the latter part of the records.

The responses of four receptors to nicotine and capsaicin were recorded. The responses of all four increased markedly after alloxan, the increase being highly significant ($P = < 0{\cdot}01$). Their responses relative to those following PDG are shown in Fig. 6. The increase in the pulmonary artery pressure and reduction in the compliance of the lungs after alloxan were similar to those described earlier (Paintal, 1969). It should be noted, however, that the increase in PCP does not affect the responses to PDG.

DISCUSSION

The results show conclusively that the responses of the J receptors (also called pulmonary C fibres; see Coleridge & Coleridge, 1984) to the three excitants PDG, nicotine and capsaicin were enhanced during pulmonary oedema produced by phosgene or alloxan (Figs 1–7). Initially we assumed that the enhancement of the responses to PDG must be due to the considerable amount of oedema-induced activity that set in gradually due to the interstitial oedema (e.g. Figs 3 and 4). However, four related sources of evidence showed that this activity was not the cause of the enhanced responses to PDG.

Firstly, in the case of thirteen receptors the increased responses to PDG occurred 2–19 min before increase in the oedema-induced activity began (e.g. see Figs 3 and 4). Secondly, the increase in the responses to PDG and the increase in oedema-induced activity were not related. Thirdly, the enhanced responses often occurred

during the silent periods of the intermittent activity in the receptors (e.g. Fig. 1). Fourthly, the bursts of intermittent activity linked to the respiratory cycle in some receptors did not enhance the responses of the receptors to PDG during the part of the respiratory cycle when the respiration-linked activity was expected to appear.

Since, as shown above, one cannot attribute the enhanced responses to PDG after phosgene to the increase in oedema-induced activity, one has to consider other possible mechanisms. One of them could be a possible potentiating effect by some mediators released in the lungs (Brocklehurst, 1976) after phosgene administration, particularly histamine since it is known that histamine potentiates the responses to PDG (Anand & Paintal, 1988), a fact confirmed in the present investigation. However, this possibility was ruled out by observing that the potentiating effect of histamine was blocked for over 30 min after prior injection of pheniramine maleate, an H_1 blocker. Thus, since the responses to PDG were recorded after injecting pheniramine maleate, one can conclude that the enhanced responses to PDG after phosgene (Figs 1–4) cannot be attributed to possible release of histamine by phosgene. A similar role of 5-HT was also excluded by observing that prior injection of 5-HT before injecting PDG did not increase the responses to PDG; in fact it actually depressed the responses of some receptors to PDG and so a potentiating role by 5-HT can be ruled out. In the same way one can rule out a similar role in the case of bradykinin as indicated by the present results.

One does not know whether the prostaglandins can potentiate the responses of the receptors to PDG (as does histamine). However, in the present experiments their possible release after phosgene was prevented by prior injection of acetylsalicylic acid (see Palmer *et al.* 1973). Thus the enhancement of the responses of the receptors to PDG after phosgene cannot be attributed to an effect by prostaglandins. However, it has not been possible to exclude all the other known mediators and leukotrienes released in the lungs (see Barnes, 1992) but one can assume, for the present, that they are unlikely to have played a major role in enhancing the responses to PDG after phosgene, since the more commonly occurring mediators, i.e. histamine, 5-HT, prostaglandins and bradykinin, have been excluded from having such a role. In view of this conclusion one has to consider the final possibility, i.e. that the increased responses of the receptors to PDG after phosgene could have been due to the increased permeability of the capillaries that phosgene is known to cause (Kennedy *et al.* 1989) and that it must have caused in the present experiments as seen by the appearance of oedemal fluid. The increased permeability could have caused more PDG to diffuse out of the capillaries to the receptor site, thereby leading to a greater excitation of the receptors by the same (i.e. control) concentration of PDG in the capillary blood. This is consistent with the fact that the responses of the receptors to the two other excitants, namely nicotine and capsaicin, were also enhanced after phosgene in the same way as the responses to PDG (Figs 6 and 7). This feature (i.e. non-specific effect) makes it unlikely that the enhancement of the responses to PDG after phosgene is due to events after the combination of the ligand drug with the membrane receptors.

The above conclusion is consistent with the observation that alloxan, another agent known to increase the permeability of pulmonary capillaries (Staub *et al.* 1967; Goetzman & Visscher, 1969), also enhanced the responses of the receptors to

PDG in a manner qualitatively similar to that following phosgene (Fig. 7); the same is true for nicotine and capsaicin qualitatively. However, the present observations showed firstly that there were considerable variations in the relative enhancement of the responses produced by them with respect to those produced by PDG. Secondly, they showed that the relative enhancement of the responses to capsaicin compared to the responses to PDG were somewhat less after alloxan compared to those after phosgene. This suggests that other factors may be involved. For example there may be variations in the type and quantity of mediators released locally after alloxan. Furthermore, although it is clear that the main effects of phosgene and alloxan involve an increase in pulmonary capillary permeability (Goetzman & Visscher, 1969; Kennedy *et al.* 1989), it should be realized that there must have been alveolar flooding in the present experiments. Therefore, the permeability of the alveolar epithelium may also have increased (see Staub, 1974). One does not know to what extent this event would affect the responses of the J receptors to the excitants.

The present study shows clearly that the responses of the J receptors to excitants are enhanced during permeability pulmonary oedema, probably due to increased permeability of the capillaries. However, it is obvious that further studies are needed, particularly for determining the relationship between the degree of increase in permeability to the degree of increase in the responses of the receptors to excitants. Additionally one needs to repeat the study to see whether there is any enhancement of the responses of the receptors to excitants during pulmonary oedema produced by methods that will not damage the capillaries, e.g. by raising pulmonary capillary pressure. If the permeability of the capillaries is not increased under such conditions one may predict that there should be no enhancement of the responses of the receptors to excitants.

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