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EFFECTS OF CAPSAICIN APPLIED PERINEURALLY TO THE VAGUS NERVE ON CARDIOVASCULAR AND RESPIRATORY FUNCTIONS IN THE CAT

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SUMMARY

1. The effects of capsaicin applied perineurally to the cervical vagus nerves have been studied on cardiovascular and respiratory functions in urethane anaesthetized cats.

2. Application of capsaicin resulted in a moderate but significant decrease in the mean arterial blood pressure and in changes of the heart rate whose direction and magnitude depended on the initial cardiac frequency.

3. Subsequent to these alterations, which may be attributed to a direct stimulation by capsaicin of vagal afferents, a transient block of impulse propagation was observed.

4. Three to five days after pre-treatment of the cervical vagus nerves with capsaicin, phenyldiguanidine and veratrine given intravenously invariably evoked bradycardia, hypotension and apnoea, while the reflex responses to intravenous injection of capsaicin and some of its pungent congeners were greatly reduced or even abolished.

5. It is suggested that vagal afferent fibres mediating cardiovascular and respiratory chemo-reflexes are separated into chemo-specifically different populations. Perineural application of capsaicin may be a useful tool for elucidating the role of different populations of peptide-containing vagal afferent fibres in the regulation of cardiovascular and respiratory functions.

INTRODUCTION

Capsaicin given to new-born rats induces selective degeneration of chemo-sensitive primary sensory neurones (Jancsó, Király & Jancsó-Gábor, 1977; Jancsó & Király, 1981) containing substance P, somatostatin, vasoactive intestinal polypeptide and cholecystokinin (Jancsó, Hökfelt, Lundberg, Király, Halász, Nilsson, Terenius, Rehfeld, Steinbusch, Verhofstad, Elde, Said & Brown, 1981; Gamse, Holzer & Lembeck, 1980), the peripheral processes of which run in the spinal and in certain cranial nerves, including the vagus nerves (Jancsó & Király, 1980).

Systemic administration of capsaicin to new-born or adult rats and to adult guinea-pigs depletes substance P and somatostatin from the vagus nerves (Gamse, Wax, Zigmond & Leeman, 1981). Recent observations have shown that in rats

capsaicin applied to a peripheral nerve induces a prolonged impairment of the function of chemo-sensitive afferent C fibres involved in the transmission of nociceptive impulses evoked by noxious heat and pain-producing chemical irritants (Jancsó *et al.* 1980). Furthermore, the local application of capsaicin to the rat sciatic nerve depletes substance P from the primary sensory neurones whose peripheral processes run in that nerve (Gamse, Petsche, Lembeck & Jancsó, 1982).

In the cat, local application of either capsaicin or substance P to the region of the nucleus of the solitary tract elicits hypotension and bradycardia. This effect of capsaicin has been attributed to the release of substance P from baroreceptor afferent nerve terminals (Haeusler & Osterwalder, 1980). However, the functional significance of the different peptide-containing afferent fibres in the vagus nerve (Lundberg, Hökfelt, Nilsson, Terenius, Elde & Said, 1978; Gamse, Lembeck & Cuello, 1979; Gilbert, Emson, Fahrenkrug, Lee, Penman & Wass, 1980; Dockray, Gregory, Tracy & Zhu, 1981) has not yet been specified.

Injection of capsaicin, phenyldiguanidine (PDG) or veratrine into the right side of the circulation induces a characteristic reflex triad consisting of bradycardia, hypotension and apnoea. The reflex effects of these compounds are mediated by different sensory receptors belonging to vagal afferent fibres. Accordingly, after intravenous (I.V.) injection capsaicin evokes the reflex triad through the excitation of pulmonary artery stretch receptors (Pórszász, Such & Pórszász-Gibiszer, 1957; Coleridge, Coleridge & Kidd, 1964; Brender & Webb-Peploe, 1969), PDG stimulates pulmonary J receptors (Paintal, 1973; Anand & Paintal, 1980) and veratrine exerts its reflex effects through the excitation of pulmonary stretch receptors and the coronary receptors of the heart (Dawes & Comroe, 1954; Aviado & Schmidt, 1955; Paintal, 1973). While the chemo-reflexes elicited by capsaicin and PDG are mediated by non-myelinated vagal afferents (Coleridge, Coleridge, Dangel, Kidd, Luck & Sleight, 1973; Paintal, 1973), those evoked by veratrine are primarily mediated by myelinated vagal afferent fibres (Paintal, 1973).

Since perineural application of capsaicin induces the selective functional impairment of certain peptide-containing non-myelinated afferent fibres (Jancsó *et al.* 1980; Gamse *et al.* 1982), the aim of the present investigation was to characterize the chemo-specificity of vagal afferent fibres by studying the effects of capsaicin applied perineurally to the cat's cervical vagus nerves on the cardiovascular and respiratory functions in acute and chronic experiments.

METHODS

The experiments were performed on thirty cats anaesthetized with urethane (1·2 g kg^{-1}, I.P.) or pentobarbitone (35 mg kg^{-1}, I.P.). The mean arterial blood pressure was recorded from the left femoral artery. The polyethylene cannula was attached through an elastic tube and via a constriction to a Statham pressure transducer (P23AA), fed by 7 Hz impulses, which was connected to an a.c. chart recorder. Respiration was recorded by a thermistor introduced into the tracheal cannula or into one nostril, and the electrocardiogram by needle electrodes inserted under the skin of the limbs. The drugs were injected in a volume of 1·0 ml. within 2 sec through a thin polyethylene cannula in the right femoral vein. PDG and veratrine were dissolved in isotonic saline. Capsaicin and its pungent congeners were dissolved in isotonic saline with ethanol and Tween 80, as described previously (Szolcsányi & Jancsó-Gábor, 1975). In some experiments the functional state of the vagus nerve was examined with stimulation by square-wave impulses (15 V, 20 Hz, 2 msec

duration). For local capsaicin treatment of the cervical vagus nerve, the previously isolated nerve was surrounded with gelatine sponge (Spongostan®, Ferrostan) strips about 3 mm wide, soaked in a 0·001–1·0 % solution of capsaicin or its solvent, which were left on the nerve for 30 min and then removed. Local treatment of both vagi can also be performed simultaneously with capsaicin solutions of lower concentrations (0·001–0·1 %). However, treatment of both vagi with a 1·0 % solution of capsaicin may be performed only if an interval of 10–15 min elapsed between the two applications, since simultaneous treatment often resulted in severe respiratory failure and/or cardiac arrest. For chronic experiments the vagus nerves were exposed under pentobarbitone anaesthesia and either treated with a 1·0 % solution of capsaicin or with its solvent as described above. After the surgical wound had been closed the animals were provided with antibiotic protection and were used 3–5 days later. The doses of the drugs used were chosen so that the resulting reflex effects would be nearly equal in size. The changes in the reflex intensities were expressed as percentages of the initial values. The results of all measurements were expressed as means ± S.E. of the mean. For statistical evaluation Student's paired t test was used.

RESULTS

Cardiovascular and respiratory effects of capsaicin applied perineurally to the vagus nerve

Application of capsaicin for 30 min to one of the vagus nerves resulted in a significant decrease in the mean arterial blood pressure compared to the control value before the application (initial value 102·95 ± 8·1 mmHg and 69·28 ± 6·13 mmHg after capsaicin; $n = 21$; $P < 0·01$). In 71 % of these experiments a pronounced reduction of the heart rate was also observed. These cardiovascular changes reached their maxima in 3·9 ± 2·2 min and gradually returned to the normal levels within the 30 min period of capsaicin application. Capsaicin was effective in concentrations of 0·001–1·0 % in producing bradycardia and hypotension, although marked differences were observed in the sensitivities of individual animals. Analysis of the effect of perineurally applied capsaicin revealed a close negative correlation between the heart rate immediately before drug application and the direction and magnitude of the changes induced (Fig. 1). A similar correlation between the initial blood pressure and its changes induced by perineural capsaicin was not established.

The alterations in the frequency and amplitude of the respiration showed considerable variability between animals. Immediately after the application of capsaicin to the vagus nerve a brief transient depression of amplitude lasting for 10–15 sec could often be observed. The respiratory frequency might be unchanged after the application (5 %) but more frequently either a decrease (in 56 % to 84·2 ± 1·9 %) or an increase (in 39 % to 140·0 ± 8·6 %) was observed ($n = 23$). There was no correlation between the initial respiratory rate and the respiratory changes. Application of the solvent to the nerve had no effect on the parameters registered.

Effects of capsaicin applied perineurally to the vagus nerve on cardiovascular and respiratory chemo-reflexes

In these experiments the effects of local treatment of both vagus nerves were studied on the cardiovascular and respiratory chemo-reflexes evoked by capsaicin and related compounds, and by PDG and veratrine. Intravenous injection of these drugs evokes a characteristic reflex triad via the excitation of different cardiopulmonary receptors whose afferents run in the vagus nerves (see Introduction).

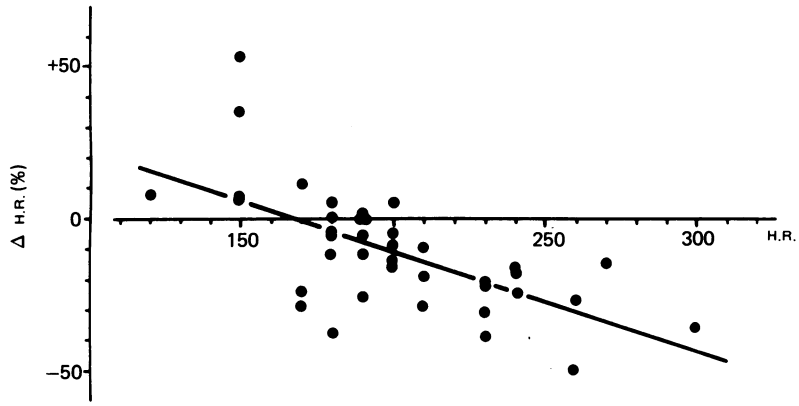

Fig. 1. Relationship between heart rate change (Δ H.R.) induced by capsaicin applied perineurally to the vagus nerve and the initial heart rate of the animal (H.R.). The heart rate changes are expressed as percentages of the control value. The regression line fits the equation: $y = -0{\cdot}3402x + 156{\cdot}65$ ($n = 39$; $r = -0{\cdot}6568$; $P < 0{\cdot}001$). The line was obtained by the method of least squares.

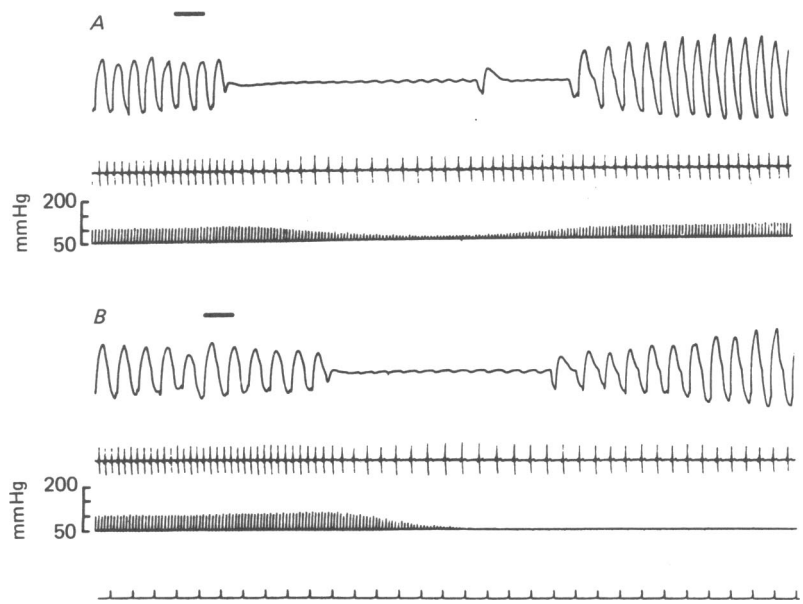

Fig. 2. Chemo-reflexes elicited by an intravenous injection of 10 μg kg^{-1} capsaicin (*A*) and 50 μg kg^{-1} PDG (*B*). The injection of the drugs is indicated by the thick signal lines. Records from above downwards: respiration, electrocardiogram, mean arterial blood pressure. Time signal, 1 sec.

Acute experiments

In control animals I.V. injection of capsaicin (5–10 μg kg^{-1}), PDG (50 μg kg^{-1}) and veratrine (10 μg kg^{-1}), elicited a characteristic reflex triad consisting of hypotension, bradycardia and apnoea (Fig. 2). Similar reflex effects followed the I.V. injection of some of the pungent congeners of capsaicin and zingerone. Thus, *N*-vanillyl-nonamide or *N*-dodecyl-homovanillamide (10–20 μg kg^{-1}), *N*-cyclohexyl-homovanillamide

TABLE 1. Cardiovascular and respiratory chemo-reflexes before (A) and 10–15 min after (B) local treatment of the cervical vagus nerves with a 0·01 % solution of capsaicin

	Heart rate		Mean arterial blood pressure		Apnoea	
Treatment	A	B	A	B	A	B
Capsaicin 10 μg kg^{-1}	46·8 ± 7·8	95·0 ± 3·8	54·2 ± 9·6	192·2 ± 11·4	9·8 ± 1·6	1·5 ± 0·8
Veratrine 10 μg kg^{-1}	51·2 ± 6·5	92·6 ± 4·7	49·9 ± 11·2	87·6 ± 7·8	4·6 ± 3·4	none
PDG 20 μg kg^{-1}	49·6 ± 6·6	94·1 ± 3·1	48·9 ± 10·9	85·3 ± 9·2	5·6 ± 3·1	1·1 ± 0·5
Noradrenaline 20 μg kg^{-1}	61·5 ± 5·7	86·2 ± 2·9	248·3 ± 8·7	254·5 ± 9·6	12·7 ± 2·8	none
Electrical stimulation of the central end of the cut left vagus nerve	65·5 ± 7·1	82·7 ± 6·8	66·6 ± 8·3	83·3 ± 7·6	8·7 ± 0·49	1·2 ± 0·25
Stretching of the common carotid arteries	56·4 ± 4·9	60·8 ± 5·3	62·5 ± 7·5	66·6 ± 6·8		
Electrical stimulation of the peripheral end of the cut right vagus nerve	35·5 ± 4·8	66·6 ± 5·3				

The changes in mean arterial blood pressure and heart rate are expressed as percentages of initial control values ± S.E. of the mean. The duration of apnoea is given in sec ± S.E. of the mean (n = 8–10).

(15–20 μg kg^{-1}) and zingerone (2–3 mg kg^{-1}) evoked the typical reflex responses, which are approximately equivalent to that after 5 μg kg^{-1} capsaicin. Local treatment of the vagus nerves with a 0·001–1·0 % solution of capsaicin partially or completely abolished the reflex effects of all the compounds tested. The effects on the chemo-reflexes evoked by capsaicin and PDG are shown in Fig. 3. Ten minutes after this treatment capsaicin still evoked a late apnoea but failed to induce changes in heart

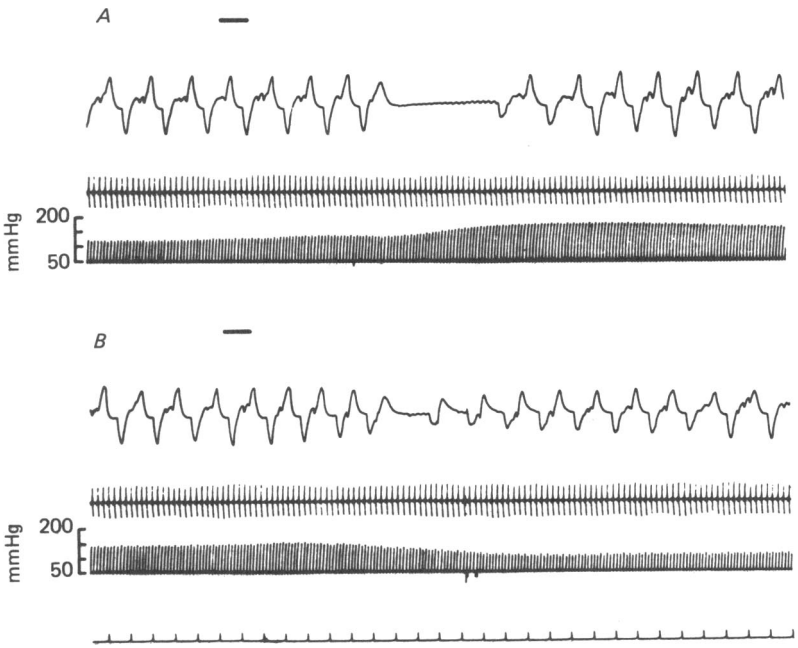

Fig. 3. Chemo-reflexes evoked by intravenous injection of 10 μg kg^{-1} capsaicin (*A*) and 50 μg kg^{-1} PDG (*B*) 10 min after the local treatment of the cervical vagal trunks with a 0·01 % solution of capsaicin. Note the nearly complete reflex blockade after the local application of capsaicin to the vagus nerves. (Experiments were performed on the same animal as shown in Fig. 2). Records from above downwards: respiration, electrocardiogram, mean arterial blood pressure. Time signal, 1 sec.

rate, and elicited a marked rise in mean arterial blood pressure. The quantitative evaluation of the effects of capsaicin, applied perineurally to the vagus nerves, on the cardiovascular and respiratory reflex responses evoked by the I.V. injection of capsaicin, PDG, veratrine and noradrenaline, and by the electrical stimulation of the vagus nerve, as well as by traction of the common carotid arteries, is presented in Table 1. Accordingly, following perineural capsaicin treatment I.V. injection of capsaicin regularly elicited a marked pressor response as found in vagotomized animals (Pórszász, György & Pórszász-Gibiszer, 1955). Furthermore, during this chemo-reflex blockade I.V. injection of noradrenaline decreased heart rate only moderately, while it caused an unchanged pressor effect. Electrical stimulation of the central end of the cut left vagus nerve distal to the site of capsaicin application, and of the distal stump of the right vagus nerve proximal to the site of capsaicin treatment resulted in smaller responses than those obtained before capsaicin treatment (see

Table 1). By contrast, stretching of the common carotid arteries resulted in a depressor response comparable to that in control animals. However, the chemo-reflexes evoked by different compounds showed a differential sensitivity towards this blocking effect of perineural capsaicin. The characteristic reflex triad could not be evoked by capsaicin, veratrine and PDG approximately 10, 14 and 20 min after a concentration of 0·01 % of capsaicin had been applied perineurally to the vagus nerves. However, the chemo-reflex blockade induced by local application of capsaicin to the vagus nerves was reversible. After removal of the capsaicin cuffs from the nerves and gentle rinsing with saline, the chemo-reflexes could again be evoked. The time needed for restoration depended on the concentration and the duration of the application of capsaicin. Hence, after the application of a 0·1 % capsaicin solution for 30 min, the intervals needed for recovery of the chemo-reflexes evoked by capsaicin, veratrine and PDG were 80–120, 70 and 60 min, respectively. 60 min after the removal of the capsaicin cuffs, the effects of noradrenaline were also fully restored. Perineural application of the solvent for capsaicin had no effect on the cardiovascular and respiratory chemo-reflexes.

Chronic experiments

After pre-treatment of the vagus nerves with a 1 % solution of capsaicin 3–5 days prior to the experiment the animals were in a good general condition and did not seem to differ in any respect from the controls. The cardiovascular and respiratory reflex responses to the I.V. injection of PDG or veratrine were practically indistinguishable from those in the controls, i.e. there was a marked fall in the mean arterial blood pressure, a reduction in heart rate, and apnoea (Figs. 4 and 5). In sharp contrast, the reflex effects of I.V. capsaicin were markedly changed. The decreases in blood pressure and heart rate evoked in control animals by the I.V. injection of 5–10 $\mu g\ kg^{-1}$ capsaicin were strongly and significantly reduced or even abolished. Moreover, capsaicin greatly increased mean arterial blood pressure, sometimes after a small fall in blood pressure, especially at higher doses (see Fig. 5). On increasing the capsaicin dose, bradycardia and apnoea could still be evoked, although these reflex effects were much smaller than in the controls. In addition, in pre-treated animals an I.V. dose of 20 $\mu g\ kg^{-1}$ or more of capsaicin could be safely injected, whereas in the controls these doses proved fatal. Besides capsaicin, other pungent agents also became ineffective in eliciting the characteristic reflex triad in pre-treated animals. However, pressor responses to *N*-vanillyl-nonamide, *N*-dodecyl-homovanillamide, *N*-cyclohexyl-homovanillamide or zingerone were significantly smaller than that induced by capsaicin (data not shown). In chronic experiments *N*-dodecyl-homovanillamide (20, 50 or 80 $\mu g\ kg^{-1}$) was ineffective or elicited only moderate increase in blood pressure.

Since lobeline has been suggested to act through the same receptors as capsaicin (Bevan, 1962), its reflex effects were also studied in chronic experiments. However, the decreases in mean arterial blood pressure and in heart rate evoked by the I.V. lobeline (100–200 $\mu g\ kg^{-1}$) were similar to those in controls ($P > 0{\cdot}1$; $n = 7$).

DISCUSSION

The effects of perineural application of capsaicin to the cat's cervical vagus nerves can clearly be separated into three phases. The first excitatory phase, lasting for about 10–15 min, is characterized by marked decreases in the mean arterial blood pressure and heart rate. This effect may be explained by a direct excitatory action of the drug

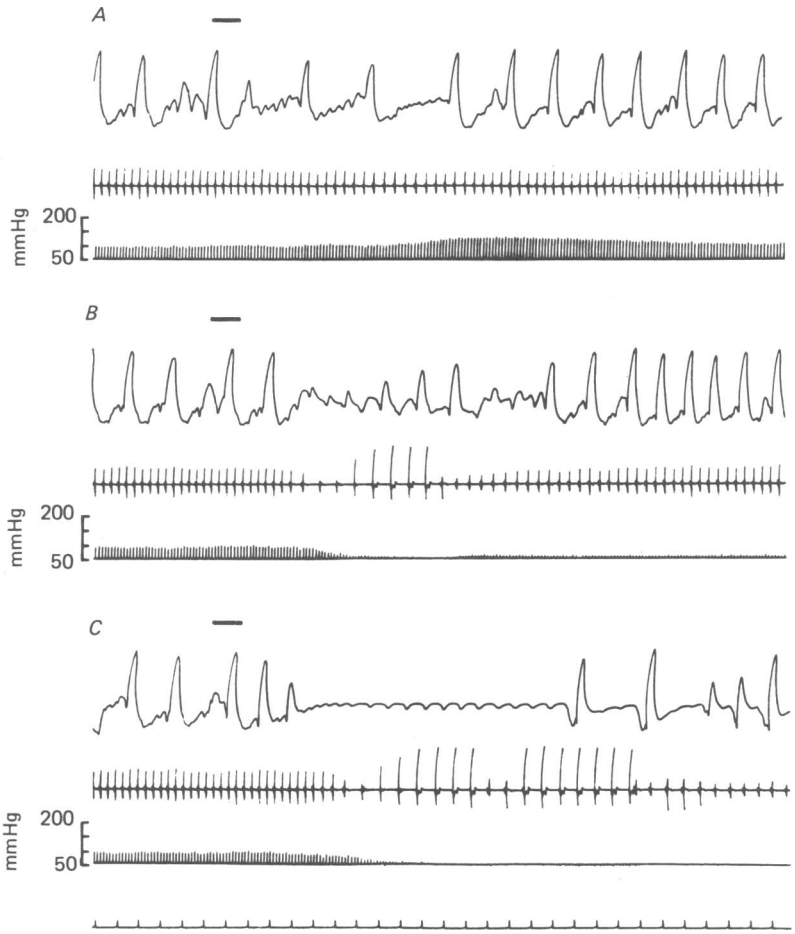

Fig. 4. Chemo-reflexes 5 days after the pre-treatment of the cervical vagus nerves with a 1% solution of capsaicin. *A*, 10 μg kg^{-1} capsaicin; *B*, 10 μg kg^{-1} veratrine; *C*, 50 μg kg^{-1}. PDG given intravenously at the thick signal lines. On the records from above downwards: respiration, electrocardiogram, mean arterial blood pressure. Time signal, 1 sec. Note that capsaicin does not evoke the characteristic reflex triad, while the effects of veratrine and PDG are the same as in the untreated animals.

on the chemo-sensitive afferent fibres in the vagus nerve (Jancsó & Király, 1980). A possible direct excitatory action of capsaicin on sensory nerves was first suggested by Baraz, Khayutin & Molnár (1968) who studied the effects of capsaicin on the viscero–sensory reflexes in the small intestine of the cat. Recent electrophysiological investigations corroborated this suggestion by showing that capsaicin depolarizes dorsal root afferent fibres of the new-born rat *in vitro* (Ault & Evans, 1980;

Yanagisawa, Nakano and Otsuka, 1980). Our electrophysiological experiments in progress show that perineural application of capsaicin (10^{-4} M) considerably increases the spike activity of the cat's vagus nerve (G. Such & G. Jancsó, in preparation).

Capsaicin applied to the vagus nerve regularly elicited a fall in blood pressure. The effect of this treatment on the heart rate depended on the initial cardiac frequency;

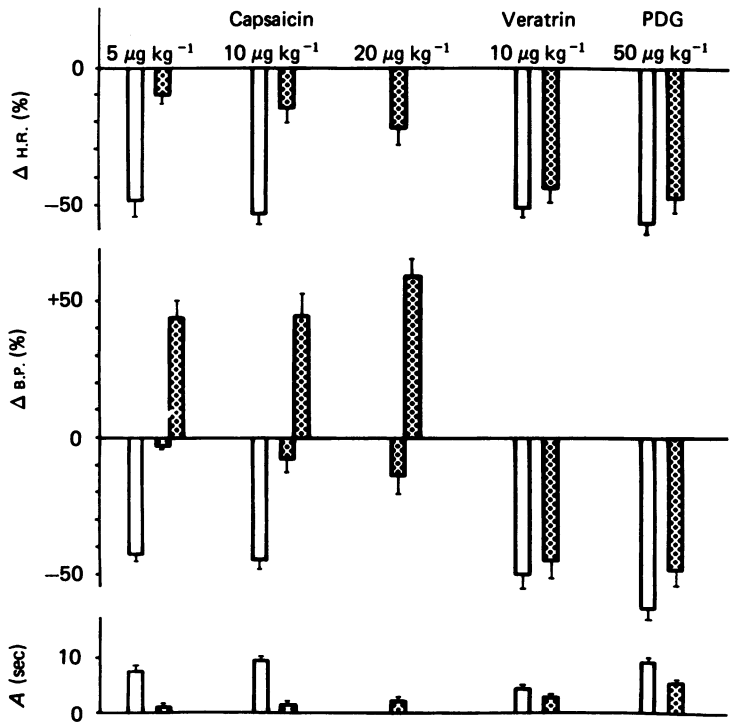

Fig. 5. Reflex responses evoked by injections of capsaicin, PDG and veratrine in control animals (open bars) and in cats whose vagus nerves had been treated with capsaicin 3–5 days prior to the experiments (filled bars). Δ H.R. and Δ B.P.: changes in heart rate and mean arterial blood pressure respectively, expressed as percentage of the initial control values. In capsaicin pre-treated animals the depressor and pressor components of the response to I.V. injection of capsaicin are shown separately. Initial control values of mean arterial blood pressure and heart rate, as determined immediately before the eliciting of the reflex responses, were $107{\cdot}21 \pm 8{\cdot}06$ mgHg and $189{\cdot}16 \pm 5{\cdot}03$ beats min^{-1} in control animals ($n = 28$) and $96{\cdot}25 \pm 3{\cdot}42$ mmHg and $192{\cdot}35 \pm 5{\cdot}29$ beats min^{-1} in capsaicin pre-treated cats ($n = 35$). *A*: duration of apnoea.

at low initial heart rates there was tachycardia, while at higher initial heart rates there was bradycardia. These effects of capsaicin closely resemble the Bainbridge reflex, the direction of which also depends on the initial heart rate and an intact vagal innervation (Coleridge & Linden, 1955; Jones, 1962).

The second phase of the effect of perineural capsaicin is characterized by a generalized blockade of vagal afferent fibres. This effect should be regarded as non-specific, since the blockade involved not only the chemo-reflexes studied but also the noradrenaline-induced reflex bradycardia. The reduced effect of noradrenaline to induce reflex bradycardia during this period may point to the possibility that

myelinated fibres may also be affected by this non-specific blockade. However, electrical stimulation of the distal end of the cut right vagus nerve above the site of capsaicin application, especially at higher intensities, as well as the stretching of the common carotid arteries may evoke bradycardia. Furthermore, the conduction of the myelinated afferent fibres was, at least in part, spared, since electrical stimulation of the proximal cut end of the nerve below the site of topical capsaicin elicited a moderate depressor and respiratory response. The mechanism whereby capsaicin blocks impulse propagation in vagal axons is at present under study in our laboratory. The results indicate that capsaicin induces a progressive but reversible local axonal block.

The third phase of the effect of perineural capsaicin develops 3–5 days after treatment. In sharp contrast to the second phase, the third phase is highly specific because only the function of afferent vagal fibres mediating the reflex effects of capsaicin and its pungent congeners is affected. Accordingly, in these animals the depressor responses elicited by the I.V. injection of capsaicin and other pungent agents, but not those evoked by PDG and veratrine were greatly reduced or even completely abolished. The moderate depressor effect observed mainly after I.V. injections of higher doses of capsaicin may be attributed to an action on the carotid sinus baroreceptors known to be stimulated by capsaicin (Pórszász *et al.* 1957; Brender & Webb-Peploe, 1960) or to some functioning afferent fibres inside the vagal trunk unaffected by the treatment. The pressor effect of capsaicin after section of the vagus nerves (Pórszász *et al.* 1955) has been attributed to a direct effect of capsaicin on vascular smooth muscle. However, the pressor effect of capsaicin may, at least in part, be reflex and mediated by afferent nerves not in the vagus nerves (Göres & Jung, 1959; Brender & Webb-Peploe, 1969).

In chronic experiments lobeline invariably elicited the reflex triad. In contrast to Bevan's (1962) assumption it may therefore be suggested that the chemo-reflexes evoked by capsaicin and lobeline are mediated by different afferent nerve fibres.

As regards the nature of the nerve fibres affected permanently and selectively by capsaicin, it can be assumed that they correspond to peptide-containing chemo-sensitive afferent nerves. This is supported by the presence of chemo-sensitive afferent fibres in the rat's vagus nerves (Jancsó & Király, 1980), a population of which contain substance P (Gamse *et al.* 1980). The possibility, however, that perineural capsaicin treatment may affect peptide-containing afferents other than those containing substance P can not be excluded, since it has been recently shown that neonatal capsaicin treatment affects somatostatin, cholecystokinin and vasoactive intestinal polypeptide-containing primary sensory neurones, as well (Jancsó *et al.* 1981). Accordingly, the selective functional impairment of vagal chemo-sensitive afferent nerves mediating the reflex effects of capsaicin and related pungent agents may be explained by the depletion of substance P and possibly other peptides from these neurones. The fact that perineural application of capsaicin to the rat's sciatic nerve induces permanent functional impairment of the chemo-sensitive afferent fibres and results in a depletion of substance P from the affected neurones (Gamse *et al.* 1982), supports this assumption.

In conclusion, the present experiments indicate that vagal afferent nerve fibres are separated into chemo-specifically different populations. One population, the function

of which can selectively and permanently be blocked by perineural capsaicin application, is composed of capsaicin-sensitive, presumably non-myelinated fibres and may be stimulated by different pungent agents through their peripheral receptors. The others, composed of both myelinated and non-myelinated afferents, are capsaicin-insensitive and may be stimulated *inter alia* by PDG or veratrine. Further studies are needed to elucidate whether these different populations of vagal afferent fibres may be correlated with the different peptide-containing nerves demonstrated in the vagus (Lundberg *et al.* 1978; Gamse *et al.* 1979; Gilbert *et al.* 1980; Dockray *et al.* 1981). Finally, the experimental approach and the data presented here may promote investigations dealing with the role of different peptide-containing afferent nerves in the regulation of cardiovascular and respiratory functions.

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