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Original articles

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APNOEIC RESPONSES TO PULMONARY AND SYSTEMIC CHALLENGE OF CAPSAICIN IN CATS.

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The contribution of sensory laryngeal and pulmonary inputs to expiratory apnoea and post-apnoeic breathing induced by capsaicin given to pulmonary circulation and to aortic arch was studied in the anaesthetized, spontaneously breathing, normoxic cats. Breathing was *via* tracheostomy. Capsaicin (10 μg(kg body wt)$^{-1}$) was injected intravenously and to the aortic arch in the intact animal, then after section of the superior laryngeal nerves, and finally after midcervical vagotomy. Capsaicin, injected as a bolus, induced expiratory arrest of breathing on both ways of injection, larger and vagally dependent ($P < 0.05$) on intravenous route, and apparently disparate in ventilatory sequence from the systemic challenge. Tidal volume was affected in the opposite direction on either route and the respiratory rate increased significantly more with an intravenous administration ($P < 0.01$). Bilateral section of the cervical vagi virtually abolished the effects of capsaicin on the breathing pattern independent of the site of challenge.

K e y w o r d s: *apnoea, control of breathing, cat, capsaicin, laryngeal afferents, vagotomy*

INTRODUCTION

The reflex respiratory and cardiovascular effects produced by injections of capsaicin — vagal C-fibre receptors stimulant, vary with the site of administration. The earliest studies (1—3) reported that in cats the ventilatory response to injection of capsaicin into right atrium was apnoea followed by rapid shallow breathing, coupled with bradycardia and hypotension, which display the pulmonary chemoreflex. Studies in dogs in which the pulmonary circulation has been isolated (4—6) and a selective pulmonary denervation performed (7) indicate that the receptors concerned in these responses resided in the lungs and are due to excitation of those attached to vagal C-fibres.

Vagotomy eliminates the constellation of pulmonary chemoreflex in cats (1, 2, 8) and dogs (7, 9, 10, 11).

Unsettled issues refer to the effects of capsaicin administered beyond the pulmonary circulation. Injection of capsaicin into the left atrium of the cat produced hyperpnoea and hypotension (1) but the pressor response was also reported (12). The triad characteristic for pulmonary chemoreflex following capsaicin challenge into the ascending aorta of the dog was evidenced by Pórszász *et al.* (13). On the contrary, solely an occasional apnoea was found to occur on left heart injection of capsaicin in this species (9, 14).

Apnoeic episodes resulting from stimulation of extrathoracic tracheal and laryngeal C-fibre receptors by capsaicin were described in the dog, rat and guinea pigs (11, 15). Activation of laryngeal sensory endings has an inhibitory effect on respiration resulting in protracted apnoea (16).

We undertook the present experiments in cats to investigate the respiratory and cardiovascular effects of capsaicin given to the aortic arch (non-pulmonary site). Thus we have attempted to compare the respiratory events to those following pulmonary C-fibre stimulation in the same animals and to assess whether the sensory inputs from the larynx and lungs contribute commensurably to the chemoreflex effects evoked by this drug.

MATERIAL AND METHODS

Ten adult cats of either gender of mean weight 3.2 kg (range 2.5—4.0 kg) were anaesthetized with an intraperitoneal (i.p.) injection of 30 mg kg^{-1} sodium pentobarbitone (Sagatal, May and Baker Ltd, UK) and later supplemented with 16 mg kg^{-1} of alpha-chloralose (Fluka AG, Switzerland) administered intravenously (i.v.) to maintain possibly constant level of surgical anaesthesia. Ethical approval for the experimental procedures used in this study was obtained from the local committee. Cats were placed supine on an operating table, brething spontaneously room air. The femoral artery was cannulated for measurement of the systemic blood pressure, and a catheter was placed in the femoral vein for injection of capsaicin and administration of additional doses of anaesthetics. In some animals right atrium was cannulated through the catheter inserted *via* an external jugular vein. In all cats a cannula was placed in the left common carotid artery reaching the aortic arch. Its position was checked *post mortem.*

The trachea was exposed through a midline incision and cannulated with polyethylene tube connected to a pneumotachograph. The flow signal was integrated electronically to obtain tidal volume. The two recurrent laryngeal nerves were identified and spared. The C_4—C_5 root of the right phrenic nerve was cleared, cut, desheathed and prepared for recording. The superior laryngeal nerves (SLNs) as well as the cervical vagi together with the aortic nerves were separated, isolated and prepared for division later in the experiment.

Arterial pressure was measured with pressure manometer (C.K. 0.1 Mera-Tronik, Poland) and blood pressure monitor (4011S MCK, Poland). Volume signals were recorded from pneumotachograph (Electrospirometer CS6, Merkury, UK). End-tidal CO_2 was measured with a capnograph (Engström Eliza plus, Gambro, Sweden). Action potentials of the phrenic nerve were amplified, filtered and integrated with a time constant of 100 ms (Neurolog System, Digitimer Ltd., UK). All recordings were registered on Omnilight recorder 8M36 (Honewell, Japan). Constant

body temperature, monitored with a rectal thermometer was maintained with a heating pad between 37—39°C throughout the experiment. Arterial blood was analysed in control conditions prior to capsaicin challenge and during the apnoea at all experimental steps. Apart from the expiratory arrests cats were normoxic. End-tidal CO_2 concentration was $4.6 \pm 0.16\%$ on average. Mean arterial blood pressure remained at about 144 ± 11.25 mmHg throughout the experiments.

Capsaicin (8-methyl-N-vanillyl-6-nonenamide, Sigma) in a dose of 10 μg kg^{-1} (0.032 μmol kg^{-1}) dissolved in isotonic saline with ethanol and Tween 80 (9) was injected as a bolus to the right femoral vein or to the right atrium and to the aortic arch. At the beginning of experiment a 0.3 ml bolus of the saline was administered to serve as a volume control. Control injection of the solution in which capsaicin was dissolved did not effect any respiratory response. All drug administrations were delivered in volume of 0.4 ml and followed by a flush of 0.4 ml saline.

The respiratory effects of capsaicin challenge into the right side of circulation and to the aortic arch were recorded in the same sequence in (1) intact animals, (2) following bilateral section of the superior laryngeal nerve and (3) after subsequent midcervical vagotomy. Injections were made at least at 15 min intervals.

Inspiratory time (T_I) and expiratory time (T_E) were determined from the start and the peak of the phrenic neurogram, and breathing frequency was computed. Prolongation of the T_E was measured as the ratio of maximal T_E during post-capsaicin apnoea or expiration ($T_{E\,test}$) to control expiration ($T_{E\,control}$), $T_{E\,test}/T_{T\,control}$. The duration of apnoeic period in phrenic activity or tidal volume was measured as the time of apnoea (respiratory inhibition).

The responses of ventilatory variables to capsaicin were assessed by comparing the mean of five breaths in restored respiration, 30 s and 60 s after the challenge to the mean of five control breaths and expressed as absolute values. Mean arterial pressure was calculated as the sum of diastolic pressure and one-third of pulse pressure. Results are quoted as the mean $\pm$S.E.

Tidal volume (V_T), respiratory rate (f) and mean arterial blood pressure were analyzed by repeated measures of 3-way Anova with injection route, time after capsaicin challenge (0, 30 s, 60 s) and denervation status (intact, SLNs cut) and (SLNs + vagi)-cut) as independent variables.

$T_{E\,test}/T_{T\,control}$ data were analyzed by 2-way Anova with injection mode (intravenous or aortic arch) and denervation status as independent variables. The significance of differences between individual experimental states was determined by post-hoc Duncan test. In all cases, a $P < 0.05$ was considered significant.

RESULTS

As no differences were found in the cardiorespiratory responses to capsaicin injected into the right atrium or to the femoral vein — the results were pooled and treated as an intravenous challenge.

Intravenous (i. v.) or aortic arch (a.a.) administration of capsaicin markedly differed in provoking of the expiratory apnoea, likewise showed disparate effects on the respiratory variables in reinitiated breathing. On an intravenous route post-capsaicin apnoea was usually associated with bradycardia and mild hypotension prior to midcervical vagotomy. Marked differences in the sensitivity of the individual animals to capsaicin resulted in variable hypotensive effects. A typical response to i. v. administration of capsaicin in the intact cat is illustrated in *Fig. 1*. The expiratory arrest of breathing emerged prior to the drop in blood pressure. Intravenous injection of capsaicin

provoked in all ten cats while intact and following division of the superior laryngeal nerves the expiratory apnoea of mean duration 8.5 ± 0.98 s and 8.7 ± 1.3 s, respectively ($n = 10$). Midcervical vagotomy abolished the occurrence of apnoea.

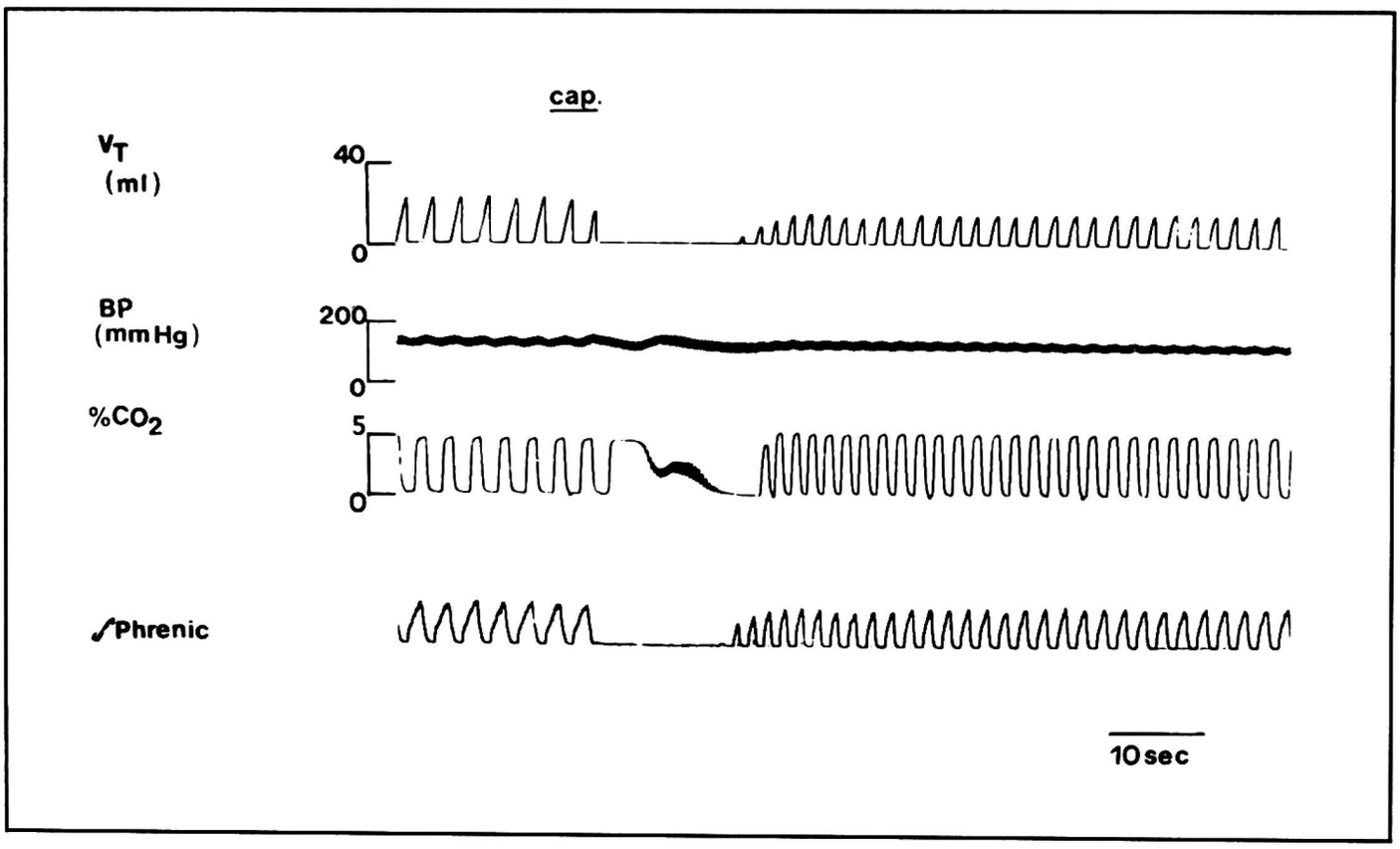

Fig. 1. Respiratory response to an intravenous injection of capsaicin in the intact cat. Capsaicin injection represented by the horizontal bar (cap). Note the expiratory apnoea coupled with mild fall in systemic blood pressure and electrical silence in the phrenic electroneurogram. Initial rapid shallow breating which follows the apnoea is associated with the decrease in tidal volume and phrenic nerve activity. V_T, tidal volume; BP, systemic blood pressure; $\%CO_2$, end-tidal CO_2; Phrenic, integrated neurogram of the phrenic nerve.

In the same cat (*Fig. 2*) after capsaicin challenge into the aortic arch the expiratory arrest of breathing was of shorter duration and was coupled with the rise in arterial blood pressure. Capsaicin given *via* this route provoked apnoea in four intact cats lasting 5.75 ± 1 s ($n = 4$), in three with divided superior laryngeal nerves persisting 8.8 ± 0.8 s ($n = 3$) and following midcervical vagotomy five cats presented apnoea of 8.6 ± 0.8 s ($n = 5$).

Such a large difference in the occurrence of apnoea on the two routes of injection of capsaicin is reflected in the mean prolongation of T_E expressed as the ratio of $T_{E\,test}$ to $T_{E\,control}$. Two-way Anova revealed significant effects of denervation status on $T_{E\,test}/T_{E\,control}$ ratio ($F_{2,10} = 4.68$, $P = 0.04$) and interaction between injection routes and denervation status ($F_{2,10} = 7.98$, $P = 0.008$) and a trend toward significant injection route ($F_{1,5} = 4.82$, $P = 0.07$). Contrast analysis exposed significantly longer duration of apnoea after intravenous injection of the drug than after aortic arch challenge in the

intact cats ($F_{1,5} = 10.3$, $P = 0.02$). There was no difference between the two routes after the division of the superior laryngeal nerves ($F_{1,5} = 4.82$, $P = 0.07$). Following midcervical vagotomy the duration of apnoea on aortic arch injection was longer at the border of statistical significance ($F_{1,5} = 6.24$, $P = 0.054$). As shown in *Fig. 3*, on intravenous injection of capsaicin prolongation of T_E was not affected by SLN_S section but abolished by midcervical vagotomy ($P = 0.02$). On aortic arch injection prolongation of T_E was present independent of the neural state.

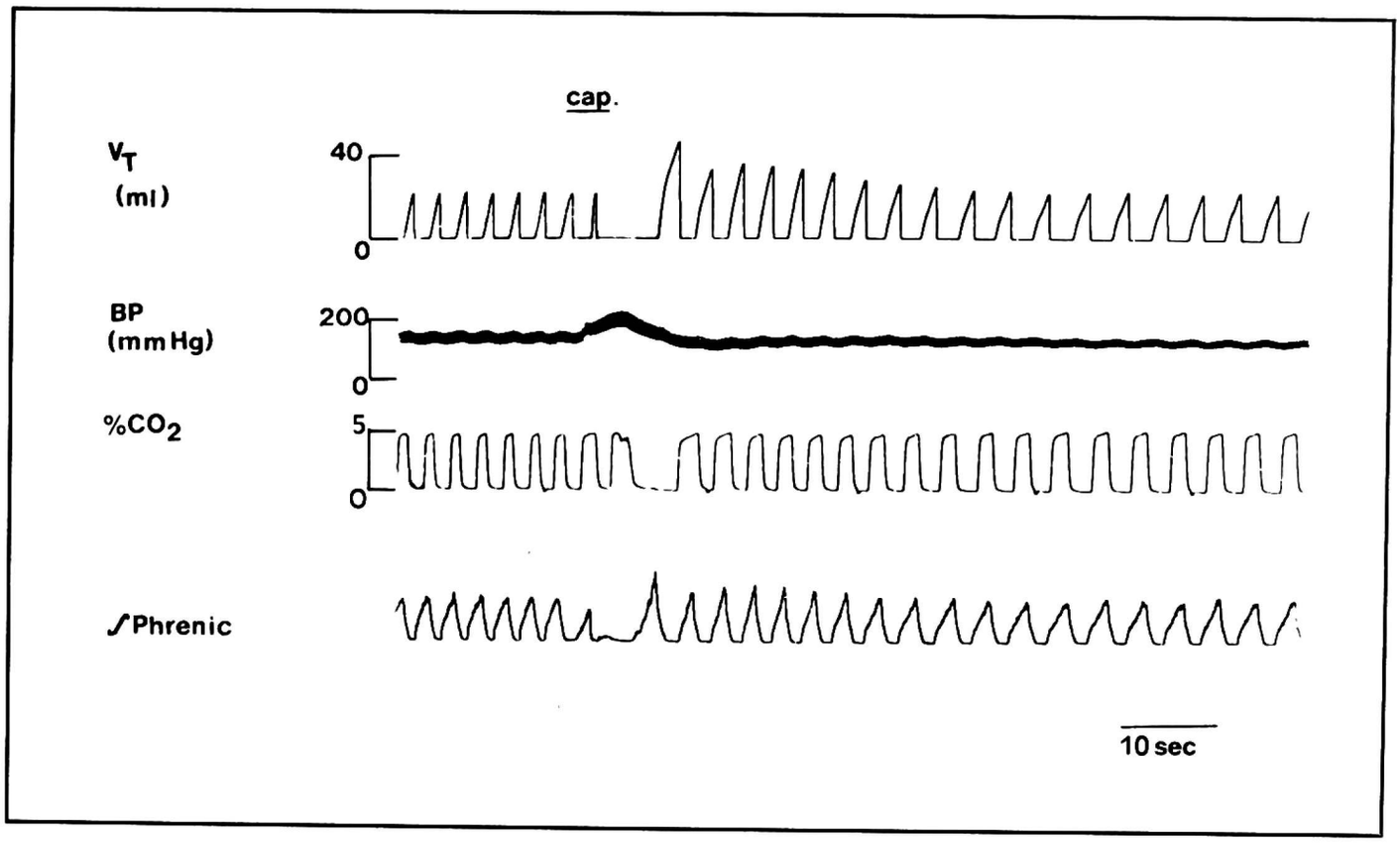

Fig. 2. Aortic arch injection of capsaicin in the same cat. Short apnoea associated with the rise in systemic blood pressure. Renewed breathing displays augmented tidal volume and increased phrenic neurogram. Traces as in *Fig. 1.*

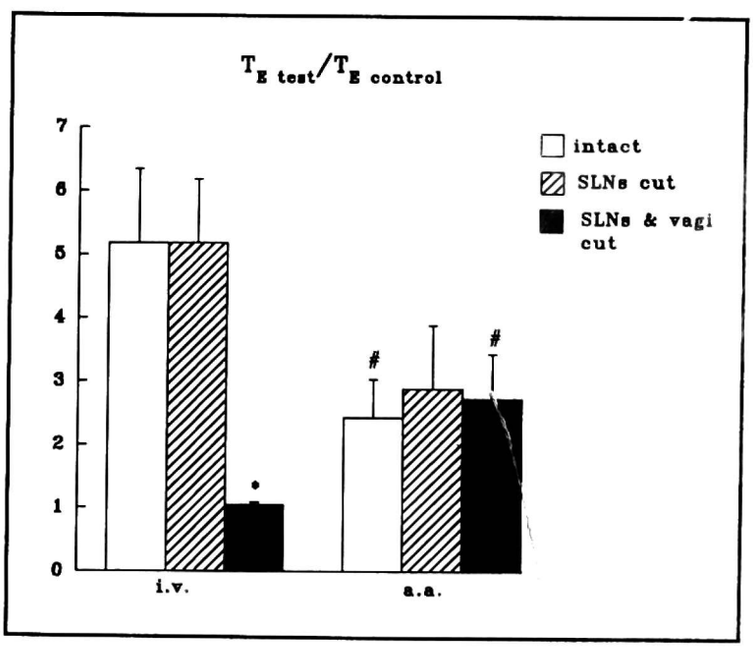

Fig. 3. Mean prolongation of T_E subsequent to an intravenous (i.v.) and aortic arch (a. a.) administration of capsaicin in intact animals and those with SLN and vagal trunks cut. Mean values ±S.E. $*P < 0.05$ compared to intact state (Duncan's test); $\#P < 0.05$ intraaortic *vs* intravenous injection (2-way Anova), $n = 6$.

Three-way Anova disclosed significant effects of injection route ($F_{1,9} = 18.23$, $P = 0.002$) and denervation status ($F_{2,18} = 56.5$, $P = 0.000001$) but no effect of drug time ($F_{3,27} = 0.99$, $P = 0.4$) on tidal volume. There were significant injection route x denervation status ($F_{2,18} = 14.2$, $P = 0.0002$) and injection route x drug time ($F_{3,27} = 7.55$, $P = 0.0008$) interactions. Moreover there were significant interactions between route of injection, denervation status and drug time ($F_{6,54} = 2.43$, $P = 0.037$). Contrast analysis exposed significant differences in tidal volume changes between the two injection routes in the intact ($F_{1,9} = 21.7$, $P = 0.001$) and SLNs cut animals ($F_{1,9} = 48.7$, $P = 0.00006$). After vagotomy the effects of capsaicin given by either route were statistically indistinguishable ($F_{1,9} = 0.15$, $P = 0.7$). As shown in *Fig. 4* capsaicin given intravenously depressed significantly tidal volume in restored breathing prior to vagotomy. Aortic arch injections of capsaicin effected insignificant increases in tidal volume.

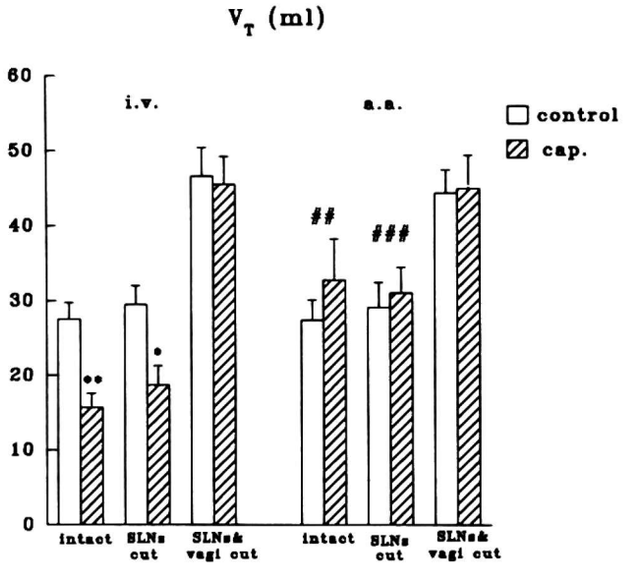

Fig. 4. The effect (mean ± S. E.) of capsaicin on tidal volume at each experimental stage and route of injection. $^{**}P < 0.01$, $^{*}P < 0.05$ compared with control values (Duncan's test); $\#\#\#P < 0.001$, $\#\#P < 0.01$ intraaortic *vs* intravenous injections (3-way Anova), $n = 10$.

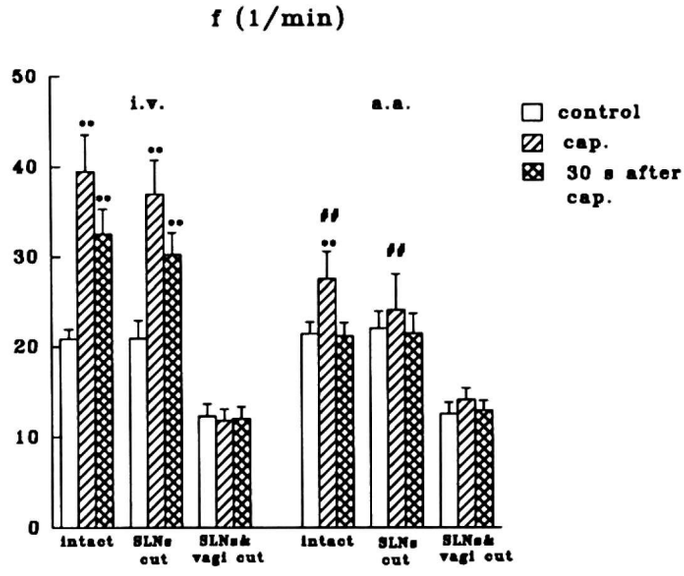

Fig. 5. Mean increases in frequency of breathing (f) on an intravenous and intraaortic administration of capsaicin in intact, SLNs cut and vagotomized animals. $^{**}P < 0.01$ compared with control values (Duncan's test); $\#\#P < 0.01$ intraaortic *vs* intravenous injection (3-way Anova), $n = 10$.

Analysis of variance yielded significant effect of injection route ($F_{1,9} = 13.9$, $P = 0.04$) and denervation status ($F_{2,18} = 58.6$, $P = 0.000001$) on respiratory rate and significant interactions between injection route and the drug time ($F_{1,18} = 22$, $P = 0.00015$) and between drug time and denervation status ($F_{6,54} = 10.4$, $P = 0.000001$). There were significant interactions between route of injection and drug time ($F_{3,27} = 7.38$, $P = 0.001$) and between route of injection, denervation status and drug time ($F_{6,54} = 9.4$, $P = 0.000001$). Contrast analysis disclosed significantly larger increase in breathing frequency

in the intact and SLNs sectioned cats given capsaicin on intravenous route compared to aortic arch challenge ($F_{1,9} = 19.5$, $P = 0.002$; $F_{1,9} = 16.4$, $P = 0.003$, respectively). Vagotomy abolished the response ($F_{1,9} = 0.86$, $P = 0.4$). As illustrated in *Fig. 5* capsaicin given intravenously increased significantly the respiratory rate in restored breathing and 30 s after the injection, prior to vagotomy. Aortic arch administration of capsaicin augmented the frequency of breathing in the intact animals only.

Three-way Anova revealed significant effect of injection route ($F_{1,7} = 22.6$, $P = 0.002$), denervation status ($F_{2,14} = 11.86$, $P = 0.0009$) and drug time ($F_{3,21} = 16.2$, $P = 0.00001$) on mean arterial pressure and significant interaction between injection route and denervation status ($F_{2,14} = 5.62$, $P = 0.02$) and injection route and drug time ($F_{3,21} = 7.24$, $P = 0.001$). There were significant interactions between route of injection, denervation status and drug time ($F_{6,42} = 2.73$, $P = 0.02$). Contrast analysis indicated significant differences in mean arterial pressure between the two injection routes in the intact ($F_{1,7} = 19.7$, $P = 0.003$) and SLNs cut animals ($F_{1,7} = 60.8$, $P = 0.0001$). Vagotomized cats treated by either challenge did not disclose statistical difference ($F_{1,7} = 1.62$, $P = 0.2$).

As shown in *Table 1* intravenous injection of capsaicin did not affect significantly mean arterial pressure in the intact ($P = 0.7$) and SLNs cut animals ($P = 0.9$). The pressor response observed following vagotomy is in line with earlier reports (1, 2, 9). Mean arterial pressure increased significantly in all neural states on aortic arch capsaicin challenge.

Table 1. Mean arterial blood pressure changes at 15 s following capsaicin injection
Data are presented as mmean ±S,E, ***P<0.001, **P < 0.01 *vs* control (Duncan test), n=8 i.v.

	i. v. MAP (mm Hg)		a. a. MAP (mm Hg)	
	control	caps.	control	caps.
intact	144.3±11.25	150.0±13.3	165.0±8.5	202.0±22.5***
SLNs cut	153.7±12.0	154.0±13.1	153.0±12.4	204.0±14.3**
vagi cut	166.5±11.5	191.3±13.5**	164.3±12.3	211.6±18.2**

DISCUSSION

Capsaicin given into pulmonary vascular bed in cats induced a pulmonary chemoreflex including apnoea, bradycardia and hypotension followed by acceleration of respiratory movements. Stimulation of vagal C-fibres by inhalation or injection of capsaicin in experimental animals results in afferent nerve conduction that elicits centrally mediated reflex change in parasympathetic and respiratory motor output (17). The latter consist of increased respiratory system resistance caused by airway smooth muscle constriction (4, 18) and immediate closure of the glottis (8, 14).

In agreement with our previous report on serotonin-induced pulmonary chemoreflex (19) we have shown that section of the superior laryngeal nerves had no effect on the expiratory inhibition of capsaicin-elicited respiratory arrest. It is possible that with the doses we used, the low concentration of capsaicin, already diluted within the right ventricle or carried by the blood stream of systemic circulation, fails to activate laryngeal C-fibre system. The latter seems to be more susceptible to aerosol and to the local instillation of the drug into the laryngeal lumen (11, 15, 20). Naida *et al.* (20) reported that perineural block of the superior laryngeal nerve by capsaicin considerably attenuated the response to intralaryngeal instillation of this drug. As noted in the introduction and reported in this study, midcervical vagotomy eliminated capsaicin-induced apnoea within reach of pulmonary circulation.

The purpose of this study was to reveal possible afferent inputs in the arrest of breathing triggered by capsaicin given to systemic circulation.

At variance with an intravenous challenge, the apnoeic spells provoked by capsaicin applied beyond the pulmonary circulation (to aortic arch) did not occur "de rigeur" in all animals and expiratory duration was apparently shorter (*Fig. 3*). Still, it persisted at similar level independent of the neural state of the animal and was not precluded by midcervical vagotomy. Capsaicin given to aortic arch may reach the bronchial arteries and stimulate bronchial C-fibre receptors, which are less responsive to capsaicin than pulmonary endings and fail to evolve the full reflex response (5). We cannot rule out the possibility that drug injected into aorta could have reached vascular endings by *vasa vasorum* arising from systemic circulation (21). Results with bronchial vasculature are more variable, possibly because their vessels drain into the pulmonary circulation and small amounts of capsaicin may reach the pulmonary vascular bed (12). Stimulation of bronchial C-fibres is known to increase the airway tone (22), which brings about variably occurring apnoeas. No studies are available showing laryngeal constriction in these respiratory arrests. In the work reported here the expiratory inhibition on injection of capsaicin into the aortic arch was maintained after vagal section. Therefore it is evident that other mechanisms come into play. One likely eplanation is that afferent neural pathway for these expiratory arrests might be attributed to vagal afferents which run in the sympathetic nerves and reach the posterior roots of the spinal nerves *via* rami communicantes (23). Besides, stimulation of C-fibres endings by capsacin in their blood supply results in local release of neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide) which have powerful constrictory effects on airway smooth muscles (17, 24). This is reinforced by the earlier evidence showing that capsaicin applied perineurally to the cervical vagus in cats blocks the capsaicin sensitive afferent C-fibres reducing or abolishing the reflex response to intravenous injection of this drug (25).

In the current experiments, prior to midcervical vagotomy, the ventilatory effects of intravenous capsaicin in renewed breathing showed depression of tidal volume and prolonged in time increase in the respiratory rate. These responses are well established and consistent with few reports which evaluated the respiratory effects of capsaicin in cats (8) and dogs (7, 10).

In our experimental design the ventilatory effects produced by injection of capsaicin into aortic arch appeared to be well contrasted from the classical pulmonary chemoreflex, which is clearly visible in *Figs 1, 2.* The findings reported here from cats are similar to the results obtained by others with capsaicin challenge to left cardiac chambers. In all our cats tidal volume showed an apparent increase, albeit not resulting in a significant hyperpnoea. This is at variance with stimulated breathing described in the same species on left ventricle injection (1). The difference may relate to the much smaller dose of the drug used in the present study. We have applied the dose of 10 μg/kg. Similar (11, 14) or larger doses (1, 5, 7, 9, 10, 18) were used by others. Initially performed dose-response analysis revealed that post-capsaicin apnoea is of similar duration for both 10 μg/kg and 20 μg/kg compared to the lowest dose of capsaicin tested (5 μg/kg). Evidence exists (20, 25) that the dosage of 10 μg/kg stimulates C-fibres only, which was our rationale to its application.

Inspection of records in the paper by Toh *et al.* (1) show inconsiderable increase in tidal volume with minute or no rise in the respiratory frequency. Injection of capsaicin into the left atrium in dogs (9) induced marked increase in respiration but tidal and timing component of the breathing pattern were not estimated.

In the current experiments injection of capsaicin into aortic arch increased the respiratory rate in the intact animals and bilateral section of the superior laryngeal nerves abolished the response. This finding is difficult to interpret as the same cats after an intravenous capsaicin challenge have augmented the frequency of breathing in both neural states (intact and following SLNs neurotomy). One possible explanation might be that massive stimulation of C-fibre receptors accessible to the pulmonary circulation and responsible for the cardiovascular and respiratory responses to capsaicin modulates the respiratory pattern *via* an afferent contribution from the vagus and to the lesser degree from its laryngeal branches. With the systemic challenge extrapulmonary airways are more accessible (26) and the influence of the laryngeal afferents may be of importance. The increase in breathing frequency on aortic route was significantly less compared to the intravenous administration. Opening of the vagal loop precluded the changes in tidal and timing component of the breathing pattern on either route of capsaicin injection (*Figs. 4, 5*). It is evident therefore, that the volume feedback from the lungs is essential to the ventilatory response to capsaicin.

It is well documented that following vagotomy administration of capsaicin into pulmonary circulation does not depress respiration and elicits a marked increase in systemic arterial pressure (1, 2, 7, 9, 11, this work). The pressor response to capsaicin injected into the right side of circulation in vagotomized animals was attributed to its direct effect on vascular smooth muscles (2). Coleridge *et al.* (9) suggested that denervation of the lungs unmasks hypertensive response from the systemic circulation.

The present report clearly shows that injection of capsaicin into aortic arch produced pressor effect both in the intact cats and those treated by midcervical vagotomy (*Table 1*). Similar observations have been made by previous workers who reported capsaicin challenge into the left cardiac chamber or into aorta (9, 12, 21). Prossor response to the aortic injection of capsaicin is probably due to stimulation of aortic bodies. Midcervical vagotomy however includes aortic neurotomy, too (27). The question of the pressor response in vagotomized cats is not easily resolvable. Most plausible possibility is to contribute it to the afferent nerves not belonging to the vagus.

In conclusion: we provided evidence that apnoea triggered by injection of capsaicin into aortic arch, as opposed to pulmonary circulation challenge, occurs variably and is carried out beyond the lung *vagi.* Afferentation from the laryngeal airway does not contribute to the respiratory inhibition. The divergent effects on tidal volume elicited on both routes of administration are mediated within the vagal pathway.

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