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INFLUENCE OF NEONATALLY ADMINISTERED CAPSAICIN ON BARORECEPTOR AND CHEMORECEPTOR REFLEXES IN THE ADULT RAT

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1 Baroreceptor and chemoreceptor reflex activity was studied in anaesthetized adult rats which had been treated neonatally with a single injection of capsaicin (50 mg/kg s.c.).

2 Pressor responses to bilateral carotid artery occlusion were significantly lower in capsaicin-treated rats compared with vehicle-treated controls. Pressor responses to intravenously injected noradrenaline were similar in the two groups of rats.

3 Resting respiratory minute volume and tidal volume were lower in anaesthetized capsaicin-treated animals than in vehicle-treated controls, but there was no significant difference in respiratory frequency.

4 The increases in respiration evoked by intravenous administration of the peripheral arterial chemoreceptor stimulant, sodium cyanide, or by breathing a hypoxic gas mixture, were significantly lower in capsaicin-treated rats compared with the controls.

5 It is concluded that baroreceptor and chemoreceptor reflex activity are significantly reduced in anaesthetized adult rats which had been treated neonatally with capsaicin, and that this is likely to result from the destruction of unmyelinated baro- and chemoreceptor afferent fibres.

Introduction

Substance P (SP)-like material is present in the carotid bodies of cats (Lundberg, Hökfelt, Fahrenkrug, Nilsson & Terenius, 1979; Cuello & McQueen, 1980; Wharton, Polak, Pearse, McGregor, Bryant, Bloom, Emson, Bisgard & Wills, 1980) and rats (Jacobowitz & Helke, 1980), in nerve fibres of the rat carotid sinus and aortic arch (Helke, O'Donohue & Jacobowitz, 1980), and in the petrosal and nodose ganglia which contain the cell bodies of baroreceptor and chemoreceptor nerves (Lundberg, Hökfelt, Nilsson, Terenius, Rehfeld, Elde & Said, 1978; Gillis, Helke, Hamilton, Norman & Jacobowitz, 1980; Helke *et al.*, 1980). SP-like material has also been detected in the nucleus tractus solitarii (NTS) of the medulla oblongata (Cuello & Kanazawa, 1978; Ljungdahl, Hökfelt & Nilsson, 1978; Helke *et al.*, 1980; Gillis *et al.*, 1980), a region where many baro- and chemoreceptor primary afferent nerves terminate (Crill & Reis, 1968; Lipski, McAllen & Spyer, 1977; Palkovits & Záborszky, 1977). Intracranial sectioning of cranial nerves IX and X, which contain baro- and chemoreceptor fibres, causes a reduction of SP-like material in the NTS (Gillis *et al.*, 1980), and microinjection of SP into the intermediate parts of the NTS has been reported to evoke hypotension and bradycardia in rats and cats (Haeusler & Osterwalder, 1980a; but cf. Talman & Reis, 1981), a response which is very similar to that obtained by activating the baroreflex. These findings have led to the suggestion that SP is a neurotransmitter at the central terminals of baro- and chemoreceptor afferent nerve endings (Gillis *et al.*, 1980; Haeusler & Osterwalder, 1980b; Helke *et al.*, 1980).

Treatment of newborn rats with capsaicin causes a degeneration of unmyelinated primary afferent neurones (Jancsó, Király & Jancsó-Gabor, 1977; Nagy, Vincent, Staines, Fibiger, Reisine & Yamamura, 1980; Scadding, 1980) and a reduction of SP-like immunoreactivity in the relay nuclei of unmyelinated afferent fibres in the central nervous system (Nagy *et al.*, 1980; Gamse, Holzer & Lembeck, 1980; Nagy, Hunt, Iversen & Emson, 1981). The SP content of other nuclei within the CNS which do not receive an unmyelinated projection of peripheral origin is not affected in animals treated neonatally with capsaicin (Gamse *et al.*, 1980; Nagy *et al.*, 1980). These observations indicate that administration of capsaicin to neonates causes the degeneration of a substantial proportion of peripheral unmyelinated afferent fibres, including those containing SP.

Among the unmyelinated afferent fibres affected by neonatal treatment with capsaicin are those which

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terminate in the sensory nuclei of cranial nerves V, IX and X (Jancsó & Király, 1980). This raises the possibility that cardiovascular control may be impaired in animals treated at birth with capsaicin, so in the course of a study on the relevance of unmyelinated afferent fibres to the mechanisms of nociception (Cervero & McRitchie, 1981), we decided to test baroreceptor and chemoreceptor reflexes in rats which had been treated neonatally with capsaicin. The objectives were to analyse the relative contribution of unmyelinated afferent fibres to these reflexes and to obtain further evidence concerning the role of SP in these sensory pathways. A preliminary account of some of the results has been published (Bond, Cervero & McQueen, 1982).

Methods

Sprague Dawley rats were used in this study. When the animals were between two and four days old they were anaesthetized with halothane (1% in oxygen) and littermates received either a single subcutaneous injection of capsaicin (50 mg/kg) or drug vehicle (1:1 polyethylene glycol 200:0.9% w/v aqueous sodium chloride). Three to seven months later the rats were used for the study of baro- and chemoreceptor reflexes. Most of the animals were males, the average body weights being 469 ± 48 g (controls) and 460 ± 47 g (capsaicin-treated).

Surgical procedures and recording techniques

Animals were anaesthetized with pentobarbitone (40 mg/kg, i.p.) and the trachea was cannulated, as were a femoral artery and vein. At the end of several experiments a catheter was also inserted into the rostral end of a common carotid artery and was used for measuring the pressure in the carotid sinus during bilateral carotid artery occlusion (BCO). Blood pressure was measured via a pressure transducer and displayed on a chart recorder (Devices, M4). Respiration was measured with an integrating pneumotachograph, as previously described (McQueen, 1973). The animals breathed either room air, 100% O_2, or a hypoxic gas mixture (10% O_2:90% N_2). Blood samples were taken from the femoral artery for the measurement of arterial blood gas tensions and pH (Radiometer BMS3).

Barorecepter function test

Bilateral carotid occlusion Rats were anaesthetized with pentobarbitone and breathed room air spontaneously. Small artery clips were applied to both common carotid arteries low in the neck for 60 s, with at least 5 min between successive occlusions. Systolic, diastolic, and mean (diastolic + $\frac{1}{3}$ pulse pressure) blood pressures were determined before bilateral carotid occlusion (BCO) and at the peak of the pressor response to BCO (Figure 1). In some experiments occlusion was maintained for 120 s, but the pressor responses were not significantly different from those obtained using the shorter period of BCO. Three occlusions were performed in each animal: before, 5 min and 30 min after a supplemental dose of anaesthetic (6 mg, i.v.) and the average rise in mean BP was calculated. The level of anaesthesia affected the basal pressure but had little influence on pressor responses in these animals. Some experiments were also performed in which a comparison was made between the pressor response observed during air-breathing with that obtained when the animal breathed 100% O_2.

Noradrenaline

The pressor responses to doses of noradrenaline injected intravenously were determined in anaesthetized rats.

Chemoreceptor function tests

Sodium cyanide The peripheral arterial chemoreceptors were activated by intravenous injection (0.1 ml + 0.2 ml wash over 2–4 s) of various doses of sodium cyanide in spontaneously breathing rats. At least 5 min was allowed to elapse between successive injections. The increase in respiratory volume during the 20 s period immediately following the injection was calculated and plotted against dose to provide a dose-response curve. Cyanide experiments were performed after testing the baroreceptors by BCO in order to minimize the total number of animals used.

Hypoxic gas After completion of the surgical procedures and before performing any other tests the animals were switched from breathing room air to breathing 10% O_2:90% N_2 for 4 min, and the reflex increase in respiratory minute volume (RMV) determined. An arterial blood sample was taken before and 3 min after changing to hypoxic gas. The level of anaesthesia (assessed qualitatively) was similar in the two groups of rats.

Drugs

The drugs used were capsaicin (8 methyl-N-vanillyl-6-nonenamide, Sigma), sodium cyanide (BDH) and (−)-noradrenaline bitartrate (Koch Light).

Statistical analysis

Differences between group means were compared by

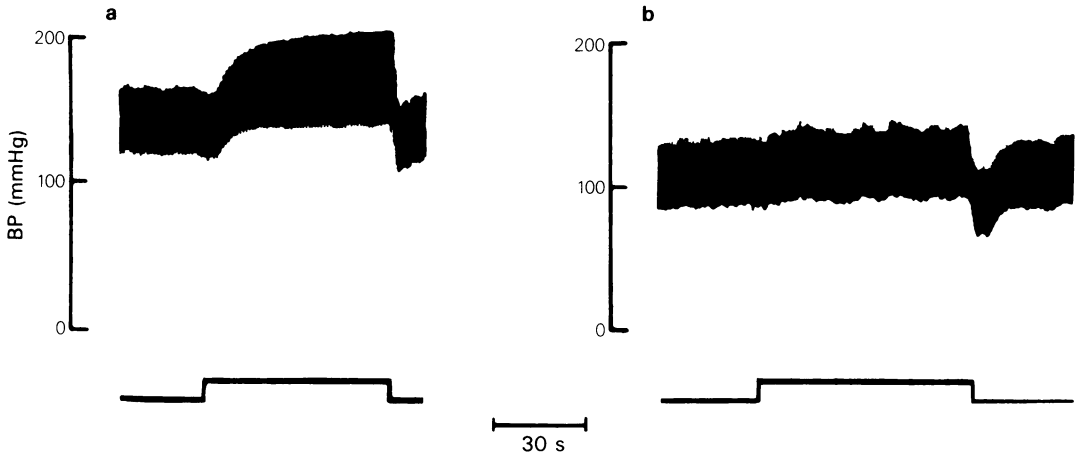

Figure 1 Pressor response to bilateral carotid occlusion (marker) in a control rat (a) compared with that obtained in a capsaicin-treated animal (b). Prolonging the period of occlusion did not significantly increase the response.

the Wilcoxon rank test, or Student's *t* test when there were insufficient data for the non-parametric test, and the null hypothesis rejected if $P<0.05$.

Results

Baroreceptor function test

Bilateral carotid occlusion Reflex pressor responses to BCO (e.g. Figure 1) were determined in ten control (vehicle-treated) rats and seven which had been treated neonatally with capsaicin. Pre-occlusion mean BP was slightly lower in the capsaicin-treated anaesthetized animals breathing air than in the controls (see Figure 2a), but this difference was not statistically significant. During BCO the averaged reflex hypertension, whether expressed in terms of mean BP (Figure 2a), systolic BP or diastolic pressure was significantly lower ($P<0.01$) in capsaicin-treated rats as compared with controls. On average the peak pressor response occurred 33.7 ± 9 s (s.e.mean) after applying the clips in control rats and 24.6 ± 7 s in capsaicin-treated animals ($P>0.05$).

In seven control and four capsaicin-treated rats a comparison was made of the pressor response to BCO during air-breathing with that obtained in the same animal while breathing 100% O_2. The results are shown in Figure 2b. Basal mean BP was higher in controls breathing O_2 than when they breathed air, but the pressor responses were not significantly different. In the case of the capsaicin-treated animals basal blood pressure was higher during O_2-breathing, but the pressor responses were not significantly different from those obtained while breathing air ($P>0.05$). On average the peak pressor response during O_2-breathing occurred 40.7 ± 8 s after applying the clips in controls and 31.7 ± 9 s in capsaicin-treated rats. The pressor responses in the controls were significantly greater than in the capsaicin-treated animals when breathing either air or oxygen ($P<0.05$).

In two rats measurements of mean carotid sinus pressure showed that pressure fell on average to 32 mmHg immediately following BCO and recovered to 50 mmHg by 30 s, at which level it remained until 60 s when the clips were removed. Cutting the

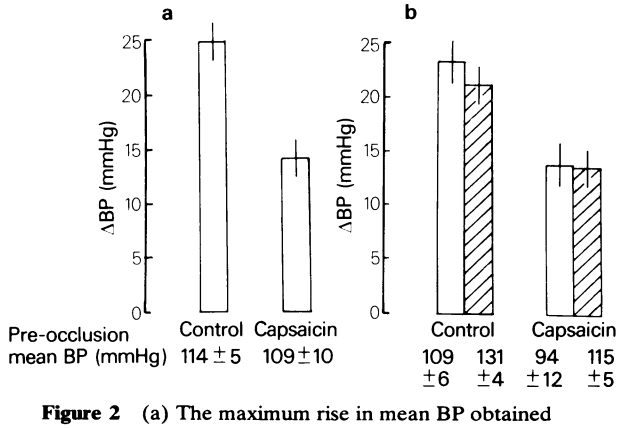

Figure 2 (a) The maximum rise in mean BP obtained during 60 s bilateral carotid occlusion (BCO) averaged from 10 control and 7 capsaicin-treated anaesthetized rats; vertical lines show s.e.mean. (b) In 7 controls and 4 capsaicin-treated animals the averaged pressor response to BCO during air-breathing (open columns) is compared to that obtained in the same animal during ventilation with 100% O_2 (hatched columns). The averaged mean BP ± s.e.mean measured just prior to BCO is given below the bar graphs.

carotid sinus nerves virtually abolished the reflex hypertension.

During the first 20 s of BCO there was a tendency for respiration to increase, particularly in control animals breathing air, but the rather variable nature of this response is reflected in the large standard errors (see Figure 3). The increase in respiration during BCO was smaller in capsaicin-treated rats and was abolished when these animals breathed 100% O_2, whereas in control rats the respiratory response to BCO was still present during O_2 breathing, although it was reduced.

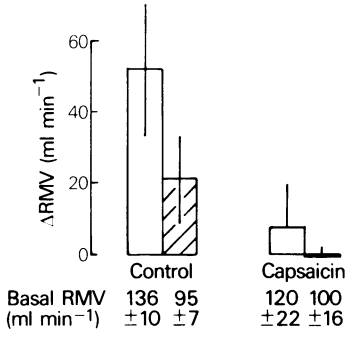

Figure 3 The averaged increase in respiratory minute volume (RMV, ± s.e.mean) observed during the first 20 s of a 60 s period of BCO during air breathing (open columns, data from 10 control and 7 capsaicin-treated rats) are shown. The hatched columns represent the respiratory change observed when 6 controls and 4 capsaicin-treated animals breathed 100% O_2. The averaged mean basal RMV ± s.e.mean measured just prior to BCO is given below the bar graphs.

Pressor responses to (−)-noradrenaline Noradrenaline was injected intravenously in two control and three capsaicin-treated rats and the averaged pressor responses evoked were plotted against the dose of noradrenaline. Results obtained are shown in Figure 4 from which it can be seen that although there may be differences between the two groups in the slopes of their dose-response lines, their pressor responses to noradrenaline (0.5–10 μg) were not significantly different ($P > 0.05$, 2-tailed t test, assuming normal distribution).

Chemoreceptor function tests

Sodium cyanide Respiratory responses to intravenous injection of various doses of the peripheral arterial chemoreceptor stimulant sodium cyanide (e.g. Figure 5) were studied in eight control and seven capsaicin-treated anaesthetized rats which were breathing air, and the results are summarized in Figure 6. Respiratory responses to cyanide were rather variable from animal to animal, as previously described (Colinet-Lagneaux, Troquet & Hermann-Gedang, 1966), and this is reflected in the rather high standard errors. The variability probably results from factors such as the level of anaesthesia, acid-base balance, and variation between individual animals in their responsiveness.

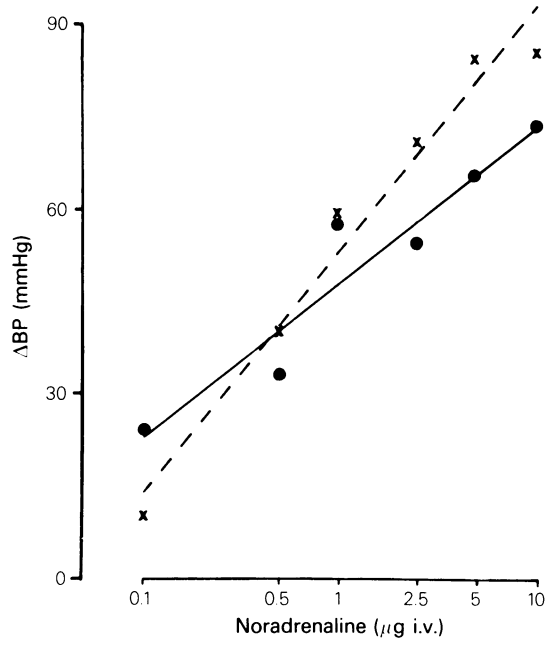

Figure 4 Averaged rise in mean BP in vehicle-treated controls (●——●, $n = 2$) and in capsaicin-treated rats (x---x, $n = 3$) plotted against dose of (−)-noradrenaline injected intravenously ($\log_{10}$ scale). Lines were fitted to the data by the method of least squares.
Mean BP measured immediately before injection of noradrenaline averaged 113 ± 4.5 mmHg in the control group and 103 ± 4 in the capsaicin-treated rats ($P > 0.05$).

Measurements made in the pre-cyanide control period showed that respiratory minute volume (RMV) and tidal volume (V_t) were significantly lower ($P < 0.01$) in the capsaicin-treated rats as compared with the vehicle-treated controls, but there was no significant difference in respiratory frequency (f) ($P > 0.05$). The mean basal values for capsaicin-treated rats (controls in brackets) were: RMV 112 ± 16 ml min^{-1} (156 ± 10); V_t 2.0 ± 0.2 (2.8 ± 0.1); f 56 ± 5 (56 ± 2) breaths min^{-1}. Control rats showed a significantly ($P < 0.05$) greater increase in RMV in response to injections of 10, 25, 50, 100 and 200 μg sodium cyanide (Figure 6). The low doses of cyanide (2.5–5 μg) had no appreciable effect on respiration in either group, whereas the very high, near-toxic, doses (400–800 μg) evoked re-

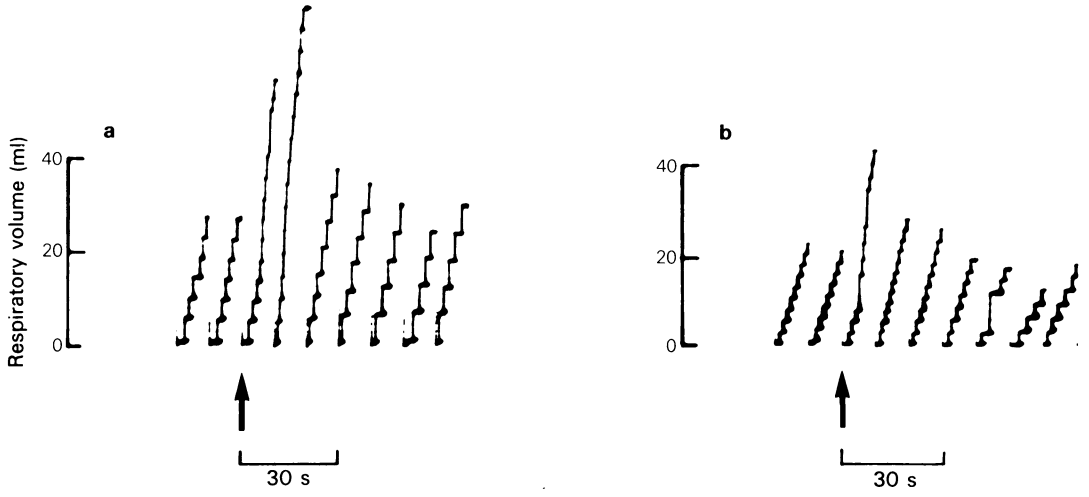

Figure 5 Respiratory response to an intravenous injection of 100 μg sodium cyanide at the arrow: (a) in a control, (b) in a capsaicin-treated rat. Each step in the ramped output from the pneumotachograph represents one breath, and the total height of each ramp is the respiratory volume in 10 s. Records read from left to right.

spiratory increases which, although greater in the control rats, were not significantly different from those obtained in capsaicin-treated animals; they caused substantial falls in BP. The increased RMV in both groups resulted from rises in f and V_t, but the latter was much more pronounced in control rats. In two control rats sodium cyanide (100 μg i.v.) evoked an increase in RMV within the first 20 s of injection which was abolished by cutting both carotid sinus nerves.

Hypoxia On switching to breathing the hypoxic gas mixture (10% O_2) an increase in respiration occurred in the two groups of rats, but both the absolute RMV and the increase in RMV were significantly greater in the controls (Table 1). Individual animals varied somewhat in their responsiveness and this is reflected in the high standard errors. The $PaCO_2$ measured during air-breathing was significantly higher in capsaicin-treated rats, as compared with the controls.

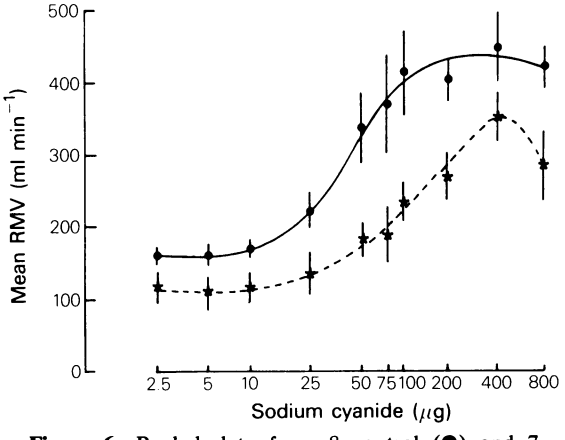

Figure 6 Pooled data from 8 control (●) and 7 capsaicin-treated rats (x) showing the mean respiratory minute volume (RMV) averaged over the first 20 s following intravenous injection of sodium cyanide (2.5–800 μg – $\log_{10}$ scale); vertical lines show s.e.mean. Lines were fitted to the data points by eye.

Discussion

Our results show that there is a significant reduction in baroreceptor and chemoreceptor reflex activity in adult rats which had been treated neonatally with capsaicin. It must be stressed that the experiments were performed under anaesthesia, so the effects we obtained may be peculiar to the anaesthetized animal. The contribution made by the anaesthetic agent could be determined by studying reflex activity in conscious capsaicin-treated rats.

Baroreceptor reflex

In a preliminary report Lorez, Haeusler & Aeppli (1981) state that treatment of neonatal rats with the same dose of capsaicin as we used did not change baroreceptor reflex function in adult animals. There was a reduction in the number of primary afferent SP-containing fibres in the rootlets of cranial nerves IX and X, but although the number of SP-containing fibres terminating in the nucleus tractus solitarius was markedly reduced in capsaicin-treated rats, SP-containing cells in this nucleus were unchanged. In the absence of more detailed information concerning

Table 1 Respiratory minute volume, arterial blood gas tensions, and pH measured in three control and three capsaicin-treated anaesthetized rats during air-breathing and again when breathing a hypoxic gas mixture (10% O_2)

		Control	*Capsaicin*
RMV (ml min^{-1})	Air	129 ± 27	93 ± 14
	10% O_2	270 ± 23	185 ± 23*
P_{aCO_2} (kPa)	Air	4.04 ± 0.12	4.67 ± 0.08*
	10% O_2	2.51 ± 0.26	3.03 ± 0.19
P_{aO_2}	Air	10.40 ± 0.40	9.83 ± 0.19
	10% O_2	5.56 ± 0.24	6.04 ± 0.32
pH	Air	7.44 ± 0.01	7.40 ± 0.03
	10% O_2	7.51 ± 0.01	7.51 ± 0.01

Respiratory volume was measured over a 10 s period starting at the peak of the respiratory response to hypoxia (49 ± 8 s after switching from air in controls, 53 ± 7 s in capsaicin-treated animals). Males were used for these tests (body weight of controls 350 ± 18 g; capsaicin-treated 342 ± 29 g). Values are expressed as means ± s.e.mean.
*$P < 0.05$ compared with vehicle-treated controls. 1 kPa = 7.5 mmHg

the experiments of Lorez *et al.*, we are unable to offer any explanation of why it is that we found a depression of baroreceptor reflex function in capsaicin-treated rats, whereas they did not.

The possibility exists that, during BCO, the fall in carotid sinus pressure might, by reducing carotid body blood flow, lead to stimulation of the carotid body chemoreceptors. This would be liable to cause reflex sympathetic vasoconstriction (McQueen & Ungar, 1971), and the pressor response to BCO might, therefore, be attributed partly to withdrawal of inhibitory baroreceptor activity and partly to chemoreceptor stimulation. Carotid chemoreceptor stimulation did seem to occur during BCO in control rats since respiration increased, albeit rather variably, when the animals were breathing air, but to a lesser extent when breathing 100% O_2, a condition in which chemoreceptor activity is greatly reduced. However, pressor responses to carotid occlusion during air-breathing were not significantly different from those obtained when on 100% O_2, and this finding suggests that the reflex rise in blood pressure was mainly due to withdrawal of baroreceptor tone. Chemoreceptor stimulation in spontaneously breathing animals is liable to activate the lung inflation reflex which can mask the primary chemoreceptor reflexes (Daly & Scott, 1962) and this might explain why the pressor response to BCO during air-breathing was no greater than obtained when the control animals breathed 100% O_2. The fact that capsaicin-treated animals showed a much smaller increase in RMV during BCO when breathing air and virtually none during O_2-breathing is consistent with a reduction in the sensitivity of their peripheral chemoreceptors.

Given that baroreflex activity was attenuated in capsaicin-treated rats, it might be considered surprising that basal BP was not elevated in these animals. However, it has to be noted that baroreflex activity had only been reduced, not abolished, and also that the animals were anaesthetized; anaesthesia can abolish the hypertension resulting from baroreceptor deafferentation in rats (De Jong & Palkovits, 1976). The similarity of control and capsaicin-treated rats in their pressor responses to noradrenaline suggests that the vascular component of the baroreceptor reflex arc was not appreciably affected by capsaicin.

Chemoreceptor reflex

Sodium cyanide is a classical stimulant of peripheral arterial chemoreceptors (see Heymans & Neil, 1958) and appears to have no direct effect on baroreceptors (McQueen, 1980a). Respiratory changes occurring soon after its intravenous administration can reasonably be attributed to stimulation of carotid body chemoreceptors since it has previously been shown, and confirmed in the present study, that the reflex increase in respiration obtained following the injection of cyanide in rats is abolished by destroying the carotid bodies or cutting the carotid sinus nerves (Colinet-Lagneaux *et al.*, 1966; Colinet-Lagneaux, Hermann-Gedang & Troquet, 1967; Sapru & Krieger, 1977).

The reflex respiratory response to intravenous sodium cyanide was significantly reduced in anaesthetized capsaicin-treated rats, and it was also found that RMV was lower and P_{aCO_2} higher than in the controls. Reflex hyperventilation in response to breathing 10% O_2 was not so pronounced in capsaicin-treated animals as in controls. However, these latter findings are difficult to interpret exclusively in terms

of reduced responsiveness to arterial chemoreceptor stimulation because in addition to stimulating peripheral chemoreceptors, systemic hypoxia may depress the CNS by a direct action. Also, reflex hyperpnoea causes a fall in Pa_{CO_2} and rise in pH which will tend to remove central respiratory drive, and the changes in blood pressure that accompany hypoxia will also indirectly influence respiration. Nevertheless, the evidence from these respiratory studies can be taken as showing that the sensitivity of the peripheral chemoreceptors and/or the central components of the reflex had been altered by capsaicin.

Substance P and unmyelinated fibres

Neonatal administration of capsaicin causes a substantial reduction in the number of unmyelinated afferent fibres, including those that originate from internal organs and terminate in the brain stem nuclei where baro- and chemoreceptor afferent fibres project (see Introduction). In preliminary studies we have found that the population of unmyelinated fibres in the carotid sinus nerves of capsaicin-treated rats is severely reduced (Cervero & McQueen, unpublished observations). Small myelinated fibres can also be affected by capsaicin at the dose used in the present study, but to a lesser extent (Nagy *et al.*, 1981). However, unmyelinated efferent fibres do not seem to be affected by neonatal capsaicin (Cervero & McRitchie, 1982), so we can therefore conclude that the changes in baroreceptor and chemoreceptor reflex function observed in the present experiments most probably result from the loss of unmyelinated afferent fibres.

SP-like material is associated with unmyelinated primary afferent fibres, including those in cranial nerves IX and X, since capsaicin treatment leads to a substantial reduction in the SP content of these fibres. Our results are not incompatible with SP having a role in the baro- and chemoreflexes by being released at the central endings of unmyelinated primary afferent fibres in the brain stem, or possibly by influencing events at the peripheral sensory endings (see McQueen, 1980b). However, it is not possible to interpret the findings in terms of a reduction in SP because neonatal capsaicin does not specifically affect SP-containing fibres; there is evidence to suggest that it can affect the levels of other peptides (e.g. somatostatin in dorsal root ganglia: Kessler & Black 1981) as well as SP. Further studies are needed to establish whether the changes in reflex activity we have observed are due to changes in SP alone, to changes in other substances, or to a combination of factors.

Treatment of neonatal animals with capsaicin may offer a preparation in which the relative contribution of myelinated and unmyelinated nerve fibres to baro- and chemoreceptor reflexes can be studied and the central interaction between the two types of fibre analyzed.

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