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CHARACTERISTICS OF C FIBRE BARORECEPTORS IN THE CAROTID SINUS OF DOGS

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SUMMARY

1. We compared the pressure–response characteristics of C fibre and A fibre baroreceptors in the carotid sinus of anaesthetized dogs, recording impulses from the sinus nerve and varying mean pressure in the vascularly isolated sinus, which was distended with a pulsatile pressure. Functional stimulus–response curves were obtained by gradually increasing sinus pressure above and decreasing it below a set-point of 100 mmHg. Baroreceptors were identified by a pulsatile discharge synchronous with the pulsations in sinus pressure. A and C fibre baroreceptors were identified by the conduction velocities and blocking temperatures of their axons.

2. The pressure–response characteristics of C and A fibre baroreceptors differed in several respects. C fibres had a pulsatile firing threshold 50 mmHg higher than that of A fibres ($105{\cdot}8 \pm 1{\cdot}8$ and $54{\cdot}6 \pm 2{\cdot}9$ mmHg, respectively), an average maximal sensitivity 35% of that of A fibres (0·39 and 1·12 impulses s^{-1} $mmHg^{-1}$, respectively), and a maximal frequency (at 220 mmHg) 29% of that of A fibres (24·5 and 84·3 impulses/s, respectively). Although invariably pulsatile at pressures above threshold, the firing pattern of C fibre baroreceptors tended to be more irregular than that of their A fibre counterparts.

3. Impulses were also recorded from C fibres that were stimulated by increasing sinus pressure but had an irregular, non-pulsatile discharge, a high pressure threshold (averaging $154{\cdot}1 \pm 7{\cdot}2$ mmHg), and a low maximum frequency ($10{\cdot}8 \pm 2{\cdot}4$ impulses/s).

4. Cooling the sinus nerve progressively attenuated conduction in both A and C fibres, A fibres being blocked between 12 and 4 °C (mean 6·8 °C) and C fibres between 4 and −1·5 °C (mean 1·0 °C). Although cooling the sinus nerve to 7 °C did not block conduction in all A fibres, impulse activity in baroreceptor A fibres at a carotid sinus pressure of 200 mmHg was no greater than that at a pressure of 75 mmHg. By contrast, at 7 °C baroreceptor C fibres still provided a signal proportional to sinus pressure.

5. Our results suggest that A and C fibre baroreceptors subserve different reflex functions, the former signalling changes in arterial pressure both above and below the normal set-point, the latter only changes above. They also suggest that differential cold blockade may be a useful tool to determine the contribution of C fibre baroreceptors to cardiovascular reflexes.

INTRODUCTION

It was suspected for many years that carotid sinus baroreceptors were of two types differing in afferent properties and fibre size (Euler, Liljestrand & Zotterman, 1941; Landgren, 1952*a*; Douglas & Ritchie, 1956; Wiemer & Kiwull, 1967). This suspicion was confirmed by Fidone & Sato (1969) who measured conduction velocities in single axons of the carotid sinus nerve in cats and showed that some baroreceptors were supplied by myelinated (A) fibres and others by non-myelinated (C) fibres. Yao & Thoren (1983) compared the afferent characteristics of the two tyes of carotid baroreceptor in rabbits and found that baroreceptors with C fibre had higher thresholds, lower firing rates, and more irregular patterns of discharge.

In the present experiments we examined the stimulus–response characteristics of C fibre baroreceptors in the carotid sinus of dogs, and compared them with those of their A fibre counterparts. Our experiments differed in several respects from those of Yao & Thoren (1983) in which carotid sinus pressure was varied by manipulating snares round the inferior vena cava and aorta. Using this technique, it is difficult to produce regular and sustained changes in sinus pressure and to control mean and pulsatile pressure independently. Moreover, the stimulus–response curves of Yao & Thoren (1983) had a maximal pressure of 150 mmHg, and we had preliminary evidence that C fibre baroreceptors in dogs did not achieve their maximal firing rates until sinus pressure was considerably above this level. By examining baroreceptor responses in the vascularly isolated sinus, we were able to regulate mean and pulse pressure independently, to extend the stimulus–response curve to 220 mmHg, and, when necessary, to maintain sinus pressure at a given level. Our experiments differed from those of Yao & Thoren (1983) in another respect. Yao & Thoren constructed their stimulus–response curves after first reducing pressure to below baroreceptor threshold. However, a response curve originating at the lower end of the baroreceptor response takes no account of the directional sensitivity or hysteresis that is an integral part of normal baroreceptor operation (Coleridge, Coleridge, Kaufman & Dangel, 1981). In our experiments, sinus pressure was increased above and decreased below a baseline of 100 mmHg, the two parts of the response curve being combined into a single curve representing the baroreceptor response to perturbations in pressure around a set-point (Coleridge *et al.* 1981).

We examined the effect of cooling the sinus nerve as a means of distinguishing A and C fibre baroreceptors, conduction in A fibres being blocked at a higher temperature than conduction in C fibres (Franz & Iggo, 1968). We also attempted to determine whether baroreceptor C fibres continued to provide the vasomotor centres with a signal proportional to carotid sinus pressure after the sinus nerve had been cooled to block input in baroreceptor A fibres.

METHODS

General

Twenty-one dogs (15–27 kg) were given promazine hydrochloride (Sparine, Wyeth, 50 mg I.M.); 30 min later they were anaesthetized with a 1:1 mixture (0·25 ml/kg I.V.) of solutions of Dial Compound (allobarbitone, 100 mg/ml, urethane, 400 mg/ml, Ciba) and sodium pentobarbitone

(50 mg/ml). Supplemental doses of anaesthetic were given as required to maintain surgical anaesthesia.

The trachea was cannulated low in the neck and the lungs were ventilated with 50% oxygen in air by a Harvard respirator (model 613) whose expiratory outlet was placed under 3–5 cm of water. Tidal P_{CO_2} was monitored by a Beckman LB-1 gas analyser, and end-expiratory P_{CO_2} was kept at about 35 mmHg by adjusting ventilator frequency. Periodically, arterial P_{O_2}, P_{CO_2}, pH and base excess were measured (Corning 175 blood gas/pH analyser). Sodium bicarbonate solution was infused I.V., when necessary, to correct metabolic acidosis.

Femoral arterial blood pressure was measured by a Statham P23Gb strain gauge. The signals representing tidal P_{CO_2}, femoral arterial blood pressure, and other variables described below (blood pressure in the isolated carotid sinus, carotid sinus baroreceptor impulse frequency and carotid sinus nerve temperature) were recorded by a Grass polygraph. Several of these variables were also recorded, together with baroreceptor action potentials, by a Gould (ES 1000) electrostatic recorder.

Control of pressure in the isolated carotid sinus

The right or left carotid sinus was isolated and perfused with arterial blood from a pressurized reservoir, as described previously (Schultz, Pisarri, Coleridge & Coleridge, 1987). Reservoir temperature was kept at 37 °C. Mean pressure in the reservoir, and hence in the carotid sinus perfusion circuit, was regulated by an inflow of compressed air and a variable leak, and was set initially at 100 mmHg. Pressure pulsations (pulse pressure, 35–45 mmHg; 100 pulses/min) were produced by a Harvard pulsatile blood pump connected to a side port on the inflow line between the reservoir and the carotid sinus. Carotid sinus pressure was measured by a Statham strain gauge (P23Gb) connected to a catheter in the lingual artery, or by a Millar micro-tip catheter transducer (model PC-340) inserted via the lingual artery.

Recording of afferent impulses

The sinus nerve was freed from connective tissue and cut near its junction with the glossopharyngeal nerve. Fine strands were dissected from the central end of the nerve and placed upon silver recording electrodes. Action potentials were amplified, displayed on an oscilloscope and recorded by the Gould electrostatic recorder. Impulse frequencies in each pressure cycle were counted by a rate-meter triggered by the perfusion pump.

Baroreceptors were identified by their pulsatile discharge synchronous with the pulsations in sinus pressure. To avoid bias towards low-threshold baroreceptors, we tested each strand for the presence of inactive high-threshold fibres by increasing mean sinus pressure from 100 to 200 mmHg. A strand containing both a low-threshold and a high-threshold fibre was subdivided, and the two fibres were examined in turn.

We measured conduction velocities in baroreceptor fibres by stimulating the sinus nerve at two points 3–5 mm apart through two pairs of electrodes fixed in a shielded assembly, deriving conduction velocity from the conduction time between the stimulating electrodes. When we were unable to mobilize a sufficient length of sinus nerve for placement on the double-stimulating-electrode assembly, we computed conduction velocity from the latency and conduction distance between a single pair of stimulating electrodes and the recording electrodes (Fig. 1) (Yao & Thoren, 1983). Owing to the short conduction distance (0·8–1·5 cm), conduction velocities of A fibres were particularly difficult to measure because the evoked potential was often lost in the stimulus artifact. In some cases, we were able to separate the evoked potential from the stimulus artifact by gradually cooling the sinus nerve (see below) between the stimulating and recording electrodes, thus decreasing the conduction velocity. Under these conditions the amplitude and configuration of the electrically evoked potential were generally similar to those of the naturally evoked potential. Once the evoked potential was identified, it was gradually restored to its original position by rewarming the sinus nerve, and the conduction velocity was determined.

Baroreceptor stimulus–response characteristics

We examined the baroreceptor stimulus–response characteristics as follows. The carotid sinus was distended with a pulsatile pressure, mean pressure being set at 100 mmHg. From this baseline, mean sinus pressure was increased slowly at the rate of 1–3 mmHg/s to a maximum of 220 mmHg and decreased at a similar rate to a minimum below the threshold of the baroreceptors, upward and

downward stimulus–response curves being obtained in random order. Pulse frequency (100 pulses/min) and pulse pressure (35–45 mmHg) were held constant. In a few experiments, pulse pressure changed slightly (by 2–5 mmHg) at very high or very low sinus pressures. Baroreceptor threshold was estimated as the lowest mean carotid sinus pressure at which a single pulse-related impulse still occurred with each pressure pulse when pressure was reduced below the baseline, and the lowest pressure at which one or more impulses occurred regularly with each pressure pulse when pressure was increased above the baseline.

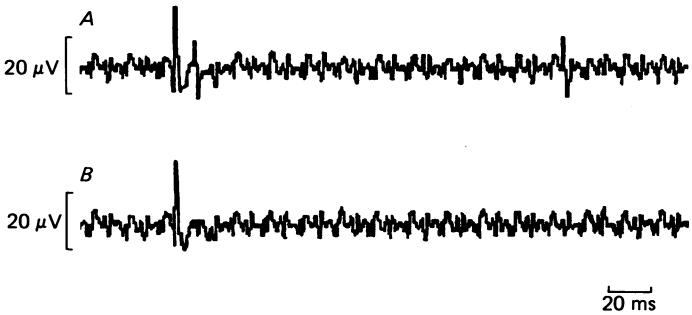

Fig. 1. Measurement of conduction velocity of baroreceptor C fibre. Note stimulus artifact in *A* and *B*. *A*, note evoked potential occurring with a latency of 8·6 ms and naturally evoked potential with similar configuration occurring some 170 ms later. *B*, cooling the sinus nerve to 0 °C between the stimulating and recording electrodes abolished the evoked potential but not the stimulus artifact. Conduction distance between stimulating and recording electrodes was 0·9 cm, and the estimated conduction velocity was 1·0 m/s.

Blocking temperature of conduction in baroreceptor fibres

We examined the effect of cooling the sinus nerve on impulse conduction in baroreceptor fibres. A short length of the sinus nerve between the carotid sinus and the recording electrodes was freed from connective tissue and placed on the platform of a silver cooling device (5 mm wide) through which alcohol of different temperatures was circulated. The sides and bottom of the platform were insulated with a layer of silicon elastomer. To reduce thermal gradients, the nerve and adjacent surface of the platform were covered with a warm (40 °C) solution of agar in saline, which upon cooling gelled to form a semisolid layer. The temperature of the platform was measured by a thermistor (Yellow Springs Instrument 729). In some experiments the sinus nerve was cooled in steps, temperature being maintained at each step for 3 min before impulse frequency was measured; in other experiments the nerve was cooled gradually from 37 to 0 °C at the rate of 2–4 °C per minute. Results obtained using the two methods of cooling were identical and have been combined. We compared the effects of cooling on conduction in baroreceptor A and C fibres while the carotid sinus was distended with a pulsatile pressure corresponding to the mid-point of the average stimulus–response curve (120 mmHg for A fibres and 160 mmHg for C fibres; see Results). We also compared the effects of cooling on baroreceptor A and C fibres at various levels of carotid sinus pressure between 75 and 200 mmHg.

Identification of A and C fibre baroreceptors

The baroreceptors fell into two groups, according to their stimulus–response characteristics. The pressure thresholds of the first group were much lower than those of the second, and maximal sensitivities and maximal firing frequencies much higher (see Results). The two groups overlapped in neither threshold, nor maximal sensitivity, nor maximal frequency. Such a sharp demarcation of afferent properties suggested that the first group of baroreceptors were supplied by myelinated (A) fibres and the second by non-myelinated (C) fibres (see Discussion). Conduction velocities in the carotid sinus nerve were often difficult to measure (see above). However, we were able to obtain satisfactory measurements in ten of thirty-seven fibres in the first group: all ten had velocities

greater than 8·0 m/s (8·1–25·1 m/s) and hence were A fibres. We were able to measure conduction velocities in twenty-one of fifty fibres in the second group: all twenty-one had velocities less than 2·5 m/s (0·5–2·3 m/s) and hence were C fibres. Since conduction in myelinated axons is blocked at a higher temperature than is conduction in non-myelinated axons (Franz & Iggo, 1968), we compared the blocking temperatures of the two groups of fibres. Of thirty fibres tested in the first group, all were blocked between 12 and 4 °C; of forty-four fibres tested in the second group, all were blocked between 4 and −0·5 °C. Taken together, these three lines of evidence (stimulus–response characteristics, fibre conduction velocities and fibre blocking temperatures) justify the conclusion that the baroreceptors were of two quite distinct types differing both in firing properties and in fibre size. Therefore, without further reservation, we shall refer to the two groups as A fibre baroreceptors and C fibre baroreceptors, respectively.

Analysis of data

Baroreceptor impulses were averaged over three to five pressure pulsations at intervals of 10 mmHg as a mean pressure was increased or decreased, and were expressed as impulses/pressure cycle and as impulses/s. We also measured the duration of each burst of impulses during the pressure pulse (burst duration) and the average discharge frequency in impulses/s during the burst (burst frequency). All values are expressed as the mean ± the standard error of the mean. Paired t tests were used to determine statistical significance; differences were considered significant if $P < 0·05$.

RESULTS

Stimulus–response characteristics of A and C fibre baroreceptors

We recorded the impulse activity of thirty-seven A fibre baroreceptors and fifty C fibre baroreceptors. When carotid sinus pressure was above threshold, all eighty-seven baroreceptors had a rhythmical discharge synchronous with the pulsations in sinus pressure (Fig. 2).

At a mean carotid sinus pressure of 100 mmHg, a pulse pressure of 35–45 mmHg, and a pulse frequency of 100 cycles/min, all thirty-seven A fibre baroreceptors were active with a firing frequency of 16·9 ± 0·7 impulses/cycle (28·2 ± 1·2 impulses/s), and no additional A fibre baroreceptors were recruited when mean sinus pressure was increased to 220 mmHg. By contrast, only twenty-four of the fifty C fibre baroreceptors were active at a mean pressure of 100 mmHg, their discharge amounting to no more than 1–3 impulses/cycle.

Threshold. Functional stimulus–response curves were obtained by changing mean sinus pressure at a constant rate (1–3 mmHg/s) above and below the baseline of 100 mmHg, pressure being increased and decreased in random order. When mean pressure was decreased from the baseline, the pulsatile firing threshold of A fibre baroreceptors (i.e. the lowest mean pressure at which a single impulse occurred with each pressure pulse) ranged from 20 to 83 mmHg, the average being 54·6 ± 2·9 mmHg (Fig. 3). When sinus pressure was reduced to 0 mmHg and then gradually returned to the baseline, A fibre baroreceptor threshold on the ascending limb of the stimulus–response curve (Fig. 4) was 43·8 ± 3·1 mmHg, i.e. an average of 11 mmHg less than that on the descending limb ($P < 0·01$).

C fibres baroreceptors had pulsatile firing thresholds much higher than those of their A fibre counterparts (Fig. 3). C fibre thresholds on the functional stimulus–response curve (i.e. as pressure was increased above and decreased below the set-point) ranged from 85 to 137 mmHg (105·8 ± 1·8 mmHg). When sinus pressure was increased above the baseline and then returned to it, the threshold on the ascending limb of the curve was less by 15·3 ± 3·1 mmHg than that on the descending limb.

Since little of the C fibre curve lay below 100 mmHg (Figs 5 and 6), the difference between the descending and ascending threshold below the baseline was small.

Three A fibre baroreceptors did not remain silent when pressure was reduced below the pulsatile firing threshold but began to fire irregularly with an overall frequency of 3–15 impulses/s. By contrast, as many as twenty-seven of the fifty C fibre

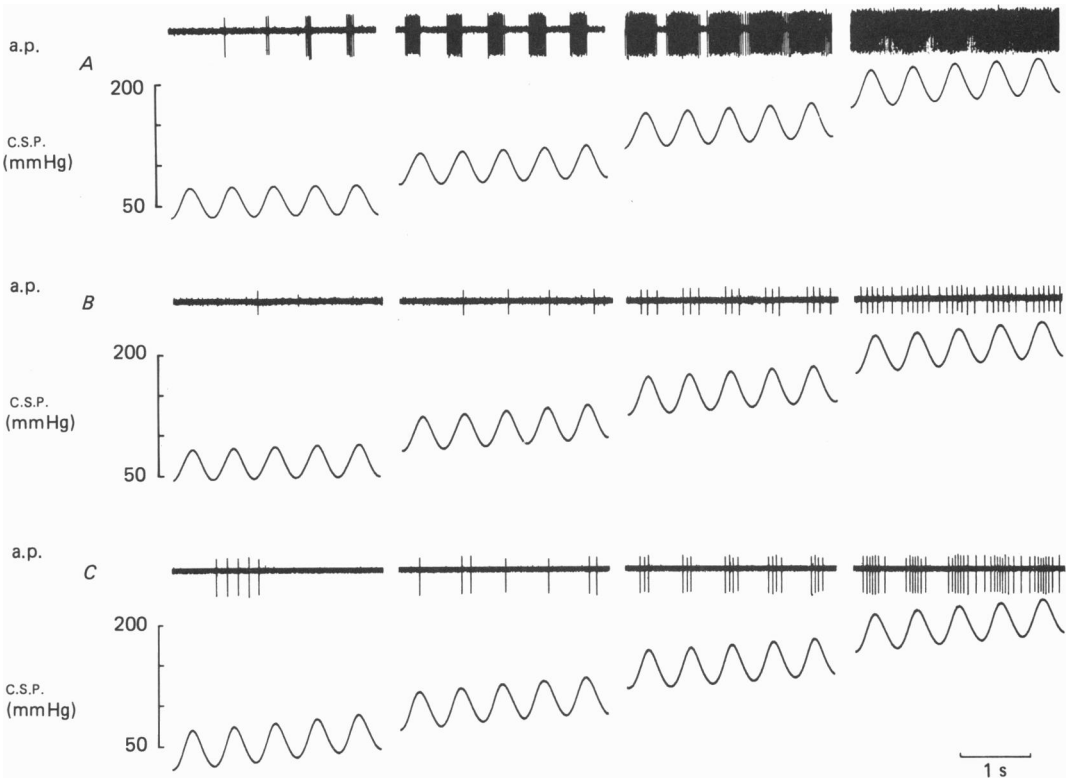

Fig. 2. Progressive stimulation of three baroreceptors as carotid sinus pressure (C.S.P.) was gradually increased from below the threshold level. *A*, action potentials (a.p.) recorded from a baroreceptor A fibre and, *B* and *C*, from two baroreceptor C fibres. Note the pulsatile nature of the discharge in both A and C fibres. The irregular activity of the C fibre baroreceptors in the first panels in *B* and *C* occurs below the pulsatile firing threshold. Note also that, at all pressures, the duration of the afferent burst, and the impulse frequency within the burst, was greater in A fibres than in C fibres.

baroreceptors displayed this paradoxical activity, firing with a sparse and usually irregular discharge (0·1–6·0 impulses/s) (Figs 2 and 5*C* and *D*); occasionally one or two impulses appeared to be pulse related. The subthreshold activity sometimes increased slightly when mean sinus pressure was reduced below 40–50 mmHg (Fig. 5*F*).

Baroreceptor responses above threshold. The response of A fibre baroreceptors to changes in pressure above the threshold level varied widely. When sinus pressure was increased above and decreased below the set-point of 100 mmHg, the average slope of individual response curves between 60 and 180 mmHg ranged from 0·45 to 1·42 impulses s^{-1} $mmHg^{-1}$. The majority (65%) of A fibre baroreceptors were maximally

sensitive over a range of pressures between 80 and 120 mmHg (Fig. 7), with maximal sensitivities ranging from 0·67 to 2·19 impulses s^{-1} $mmHg^{-1}$.

All A fibre baroreceptors demonstrated directional sensitivity, i.e. when pressure was varied above and below the set-point, impulse frequency on the ascending limb of the stimulus–response curve was invariably higher than that at the corresponding

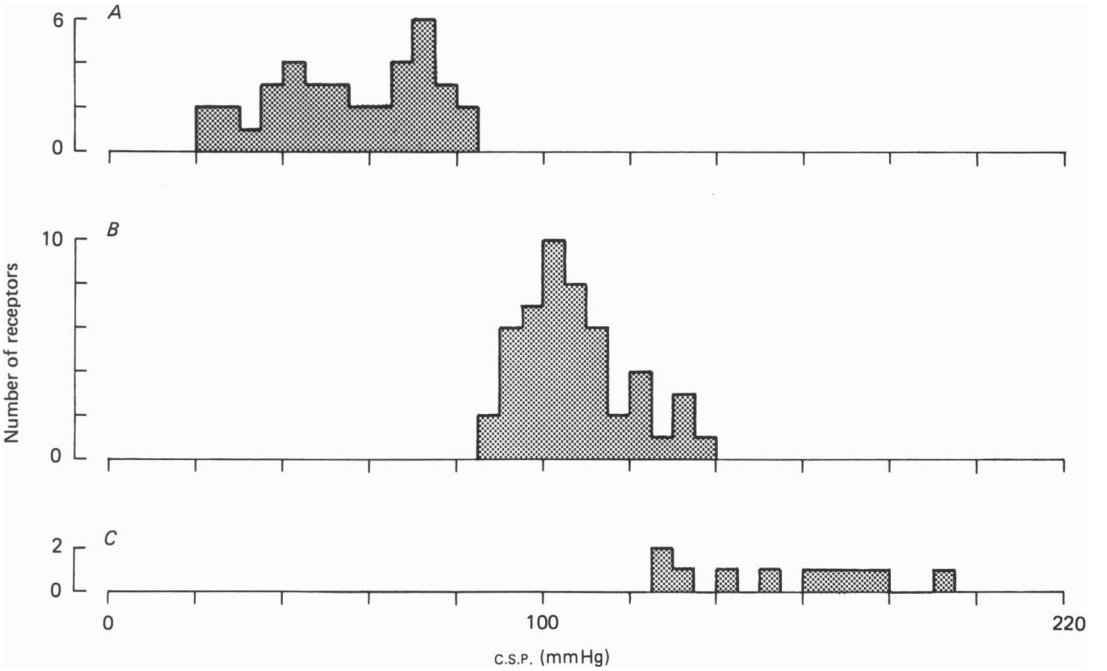

Fig. 3. Distribution of the threshold pressures for activation of ninety-seven carotid sinus receptors. *A*, thirty-seven A fibre baroreceptors; *B*, fifty C fibre baroreceptors; *C*, ten endings firing with an irregular, non-pulsatile discharge. Thresholds were determined by increasing carotid sinus pressure (C.S.P.) above and decreasing it below the baseline (set-point) of 100 mmHg.

pressure on the descending limb (Fig. 4). All but two of the thirty-seven curves had a clear upper point of inflexion (Fig. 4). The inflexion points of three curves were between 120 and 140 mmHg, of ten between 140 and 160 mmHg, of fourteen between 160 and 180 mmHg, of six between 180 and 200 mmHg and of two between 200 and 220 mmHg.

From these individual responses we plotted the average functional stimulus–response curve for the whole group of thirty-seven A fibre baroreceptors (Fig. 6). The downward and upward parts together formed a curve of sigmoid shape whose steepest part between 80 and 120 mmHg had an average slope of 0·85 impulses s^{-1} $mmHg^{-1}$. At the maximal pressure of 220 mmHg, the firing frequency of A fibre baroreceptors averaged 84·3 $\pm$ 4·5 impulses/s (range, 47–172 impulses/s).

C fibre baroreceptors not only had an average pulsatile firing threshold more than 50 mmHg higher than that of A fibre baroreceptors, their overall firing rates were considerably less. Thus the slope of individual C fibre response curves between 100

and 200 mmHg ranged from 0·03 to 0·33 impulses s^{-1} $mmHg^{-1}$. The majority (70%) of C fibre baroreceptors were maximally sensitive over a range of pressures between 140 and 200 mmHg (Fig. 7), with maximal sensitivities ranging from 0·17 to 0·67 impulses s^{-1} $mmHg^{-1}$.

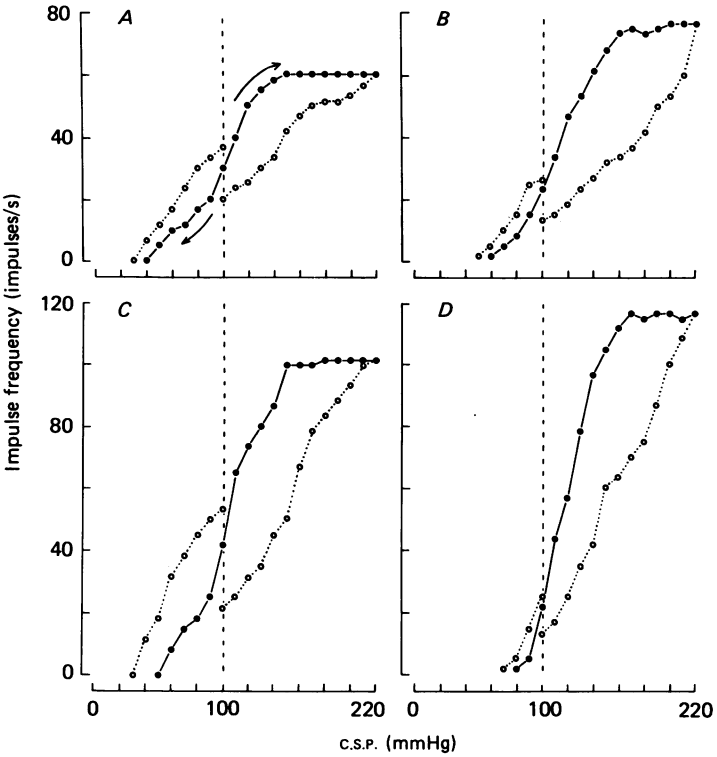

Fig. 4. Functional stimulus–response curves of four A fibre baroreceptors, illustrating the range of baroreceptor responses. C.S.P., mean carotid sinus pressure. ● and continuous lines, baroreceptor responses as pressure was increased and decreased (see arrows in *A*) from the baseline of 100 mmHg (vertical dashed line); ○ and dotted lines, baroreceptor responses as pressure was returned to the baseline. Note point of inflexion in the upper part of each ascending curve.

All C fibre baroreceptors showed directional sensitivity (Fig. 5). In contrast to their A fibre counterparts, half of the C fibre baroreceptors had no clear upper point of inflexion, their activity continuing to increase as pressure was raised to the maximum of 220 mmHg (Fig. 5). However, obvious inflexions were present in twenty-five of the curves (three between 160 and 180 mmHg; eight between 180 and 200 mmHg; and fourteen between 200 and and 220 mmHg).

The average stimulus–response curve of the whole group of fifty C fibre baroreceptors was less obviously sigmoid than the A fibre curve (Fig. 6); its steepest part, which occurred between 160 and 200 mmHg, had a slope of 0·23 impulses s^{-1} $mmHg^{-1}$. At the maximal pressure of 220 mmHg, firing frequencies averaged $24·5 \pm 1·2$ impulses/s (range 5–40).

Burst frequency and burst duration. As carotid sinus pressure increased, the

duration of each pulse-related burst of impulses (burst duration) and the average impulse frequency during the burst (burst frequency) increased (Table 1). In the case of A fibre baroreceptors, both burst duration and burst frequency increased with sinus pressure until, at a pressure of 160 mmHg, firing became continuous and burst

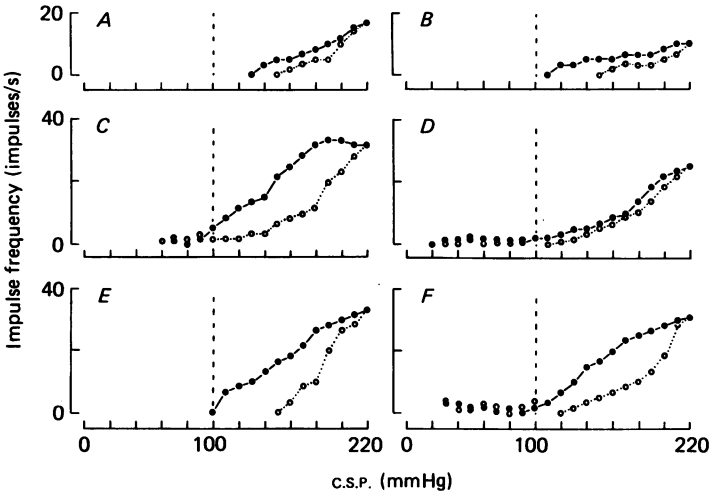

Fig. 5. Functional stimulus–response curves of six C fibre baroreceptors. C.S.P., carotid sinus pressure. ● and continuous line, baroreceptor responses as pressure was increased and decreased from the baseline of 100 mmHg (vertical dashed line); ○ and dotted line, baroreceptor responses as pressure was returned to the baseline. In *C*, *D* and *F*, the points not joined by continuous or dotted lines indicate irregular baroreceptor activity occurring below the pulsatile firing threshold. Note that an inflexion in the upper part of the ascending curve is obvious only in *C*.

duration was equal to the duration of the pressure cycle. Thereafter, any further increase in A fibre baroreceptor firing was due to increasing burst frequency. Over the firing range of A fibre baroreceptors (40–220 mmHg), burst frequency increased twofold and burst duration thirtyfold (Table 1).

By contrast, although a few C fibre baroreceptors demonstrated appreciable increases in burst frequency (Fig. 2*C*), the great majority did not (Fig. 2*B*), and, overall, increases in C fibre baroreceptor firing were dependent largely upon increased burst duration. Thus, over the firing range of C fibre baroreceptors (100–220 mmHg), burst duration increased eightfold but burst frequency by only 16% (Table 1).

Regularity of discharge. A and C fibre baroreceptors also differed in the regularity of their discharge pattern. The A fibre baroreceptors showed a generally regular and progressive increase in impulse frequency as carotid sinus pressure increased. By contrast, although C fibre baroreceptor firing increased overall as pressure increased (Figs 5 and 6), and above threshold was always pulse related, it often did not follow faithfully the pulse by pulse increase in pressure (Fig. 2*C*, second panel). The greater pulse by pulse variability of C fibre baroreceptor firing was also demonstrated by comparing the coefficients of variation (ratio of standard deviation to the mean) for A and C fibre impulse frequencies at several levels of sinus pressure, mean and pulse pressure being constant at each level (Table 2). In both A and C fibres, the pulse by

pulse variability of discharge decreased as pressure, and hence impulse frequency, increased, but the coefficient of variation was not simply an inverse function of impulse frequency. Thus although the average impulse frequency (7·5 impulses/cycle) in C fibres at a carotid sinus pressure of 160 mmHg was comparable to that in A fibres (6·9 impulses/cycle) at a pressure of 80 mmHg, the firing frequency in C fibres had a variability five times that in A fibres (Table 2).

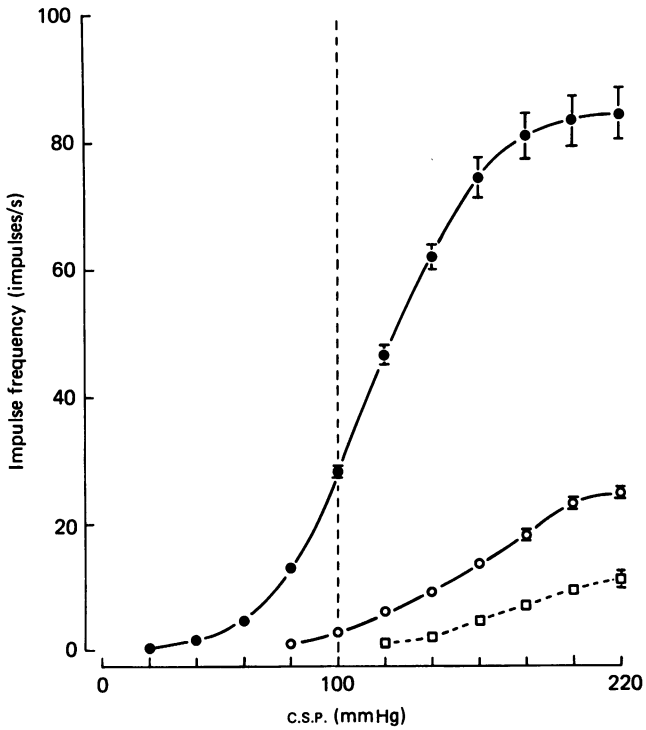

Fig. 6. Functional stimulus–response curves of thirty-seven A fibre baroreceptors (●) and fifty C fibre baroreceptors (○) (means ± S.E.M.); the two curves (continuous lines) were obtained by increasing carotid sinus pressure (C.S.P.) above and decreasing it below the baseline of 100 mmHg (vertical dashed line). □ and dotted line, response of ten irregularly firing fibres as pressure was gradually increased above the baseline.

Fibres with an irregular discharge

We also recorded impulses from ten fibres that were stimulated by increasing sinus pressure but never acquired a regular pulse-related discharge, even when the carotid sinus was distended with a pulsatile pressure around a mean of 220 mmHg (Fig. 8). Occasionally these fibres fired in brief bursts of one to four impulses, but such sporadic activity was not related systematically to the pulsations in sinus pressure, for it occurred during the 'systolic' phase of some pressure pulses and during the 'diastolic' phase of others (Fig. 8*A* and *B*). Some of these irregularly firing fibres were silent over the lower range of sinus pressure and began to fire when pressure reached a certain level, so that their threshold was readily determined (Fig. 8*A*). Others fired irregularly at lower pressures but impulse frequency was unrelated to

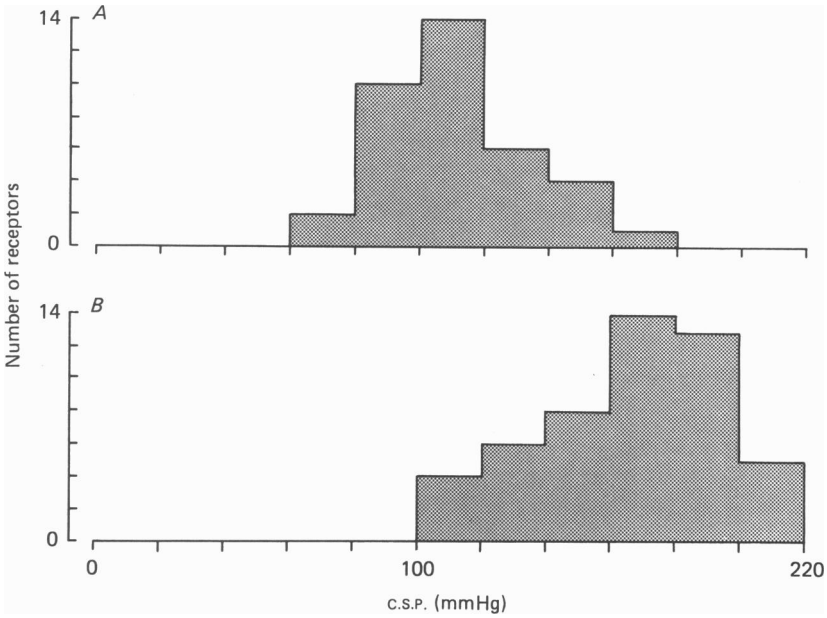

Fig. 7. Distribution of pressures at which baroreceptors were maximally sensitive: *A*, thirty-seven A fibre baroreceptors; *B*, fifty C fibre baroreceptors. The 20 mmHg range of pressure over which each baroreceptor was most sensitive was determined from the slope of the stimulus–response curve as carotid sinus pressure (C.S.P.) was increased above and decreased below the set-point of 100 mmHg.

TABLE 1. Effect of carotid sinus pressure on burst frequency and burst duration of A and C fibre baroreceptors

	A fibres		C fibres	
C.S.P. (mmHg)	Burst frequency (impulses/s)	Burst duration (s)	Burst frequency (impulses/s)	Burst duration (s)
40	43·2 ± 3·8	0·02 ± 0·01	—	—
60	47·3 ± 2·0	0·06 ± 0·02	—	—
80	51·7 ± 2·5	0·16 ± 0·03	—	—
100	65·7 ± 2·5	0·26 ± 0·02	22·7 ± 0·7	0·07 ± 0·01
120	72·9 ± 2·8	0·40 ± 0·02	24·4 ± 0·7	0·14 ± 0·01
140	73·0 ± 2·9	0·53 ± 0·02	25·0 ± 0·8	0·23 ± 0·02
160	74·5 ± 2·8	0·60	25·3 ± 0·8	0·32 ± 0·03
180	81·1 ± 3·5	0·60	25·0 ± 0·7	0·44 ± 0·03
200	83·4 ± 3·9	0·60	26·0 ± 0·9	0·52 ± 0·02
220	84·3 ± 4·5	0·60	26·3 ± 1·0	0·55 ± 0·02

Data (means ± S.E. of the means) represent activity of thirty-seven A fibre and fifty C fibre baroreceptors at various levels of mean carotid sinus pressure (C.S.P.); pulse pressure (40 mmHg) and pulse frequency (100 pulses/min) were held constant. Irregular activity below the pulsatile firing threshold is not included. As carotid sinus pressure increases, both burst frequency (i.e. impulse frequency averaged over the burst) and the duration of the burst increase. Note that when pressure reaches 160 mmHg the duration of the A fibre baroreceptor burst equals the duration of the pressure cycle (0·6 s).

TABLE. 2. Coefficients of variation of impulse activity in baroreceptor A and C fibres at different levels of mean carotid sinus pressure

	A fibres		C fibres	
C.S.P. (mmHg)	Impulse frequency (impulses/cycle)	Coefficient of variation (%)	Impulse frequency (impulses/cycle)	Coefficient of variation (%)
80	6·9 ± 1·3	2·3 ± 1·2	—	—
100	14·4 ± 1·3	1·7 ± 0·7	1·2 ± 0·3	49·3 ± 5·9
120	27·0 ± 3·2	1·4 ± 0·7	3·5 ± 0·5	30·6 ± 6·3
160	39·8 ± 5·5	1·0 ± 0·3	7·5 ± 1·3	11·2 ± 2·3
200	45·3 ± 4·1	0·8 ± 0·3	12·0 ± 1·4	6·2 ± 1·1

Data (means ± S.E. of the means) represent impulse frequencies (impulses/cycle) and coefficients of variation (%) of firing in six baroreceptor A fibres and ten baroreceptor C fibres. Impulse frequencies in individual fibres counted over ten pressure cycles at several levels of mean carotid sinus pressure (C.S.P.); pulse pressure and pulse frequency held constant. The coefficient of variation calculated for each fibre at each level of sinus pressure.

pressure, being no higher at 120 mmHg than at 20 mmHg. When pressure reached threshold, however, there was an obvious inflexion in the stimulus–response curve, and discharge frequency began to increase (Fig. 8*C*). In repeated tests on a given fibre, threshold sometimes varied by as much as ± 10–20 mmHg, and we have taken the average. Threshold pressures of these ten fibres ranged from 127 to 190 mmHg

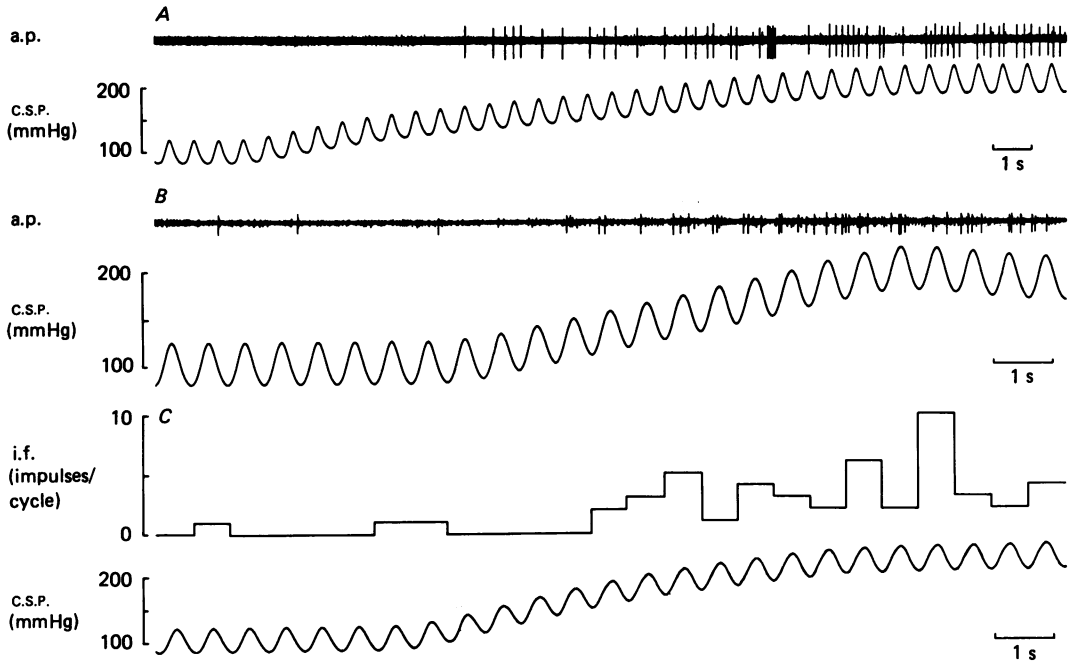

Fig. 8. Response of three irregularly firing fibres to increasing carotid sinus pressure (*A*, *B* and *C*, recorded in different dogs). a.p., action potentials; i.f., impulse frequency (impulses/pressure cycle, recorded by rate-meter); C.S.P., carotid sinus pressure.

(average 154·1 ± 7·2 mmHg) and were thus higher than those of all but five of the fifty rhythmically firing C fibre baroreceptors (Fig. 3). Above threshold, activity was directly, if irregularly, related to sinus pressure (Fig. 8). Maximal frequencies at a pressure of 220 mmHg ranged from 5 to 18 impulses/s (10·8 ± 2·4 impulses/s). The average stimulus–response curve of these fibres is depicted in Fig. 6. Five of the irregularly firing fibres appeared to be non-myelinated, two having conduction velocities of less than 2·5 m/s and three having blocking temperatures below 4 °C (see below).

Effects of cooling the carotid sinus nerve

We examined the effects of cooling the sinus nerve on baroreceptor impulse activity recorded central to the cooling platform (Figs 9 and 10), the carotid sinus being distended with a pulsatile pressure around a mean corresponding to the mid-point of the average stimulus–response curve (A fibres, 120 mmHg; C fibres, 160 mmHg). We determined the blocking temperature of seventy-four baroreceptor fibres in order to identify A and C fibres (see Methods). We also examined the gradual attenuation of impulse conduction in sixty-four baroreceptor fibres (twenty-seven A

fibres, thirty-seven C fibres) as the sinus nerve was cooled progressively (Figs 9 and 10). Effects of cooling on individual fibres varied widely. For example, conduction in one A fibre was blocked over a narrow range of temperature, being unimpaired at 15 °C and blocked totally at 9 °C, whereas conduction in another A fibre was attenuated gradually between 15 and 4 °C. However, the average cooling curves of

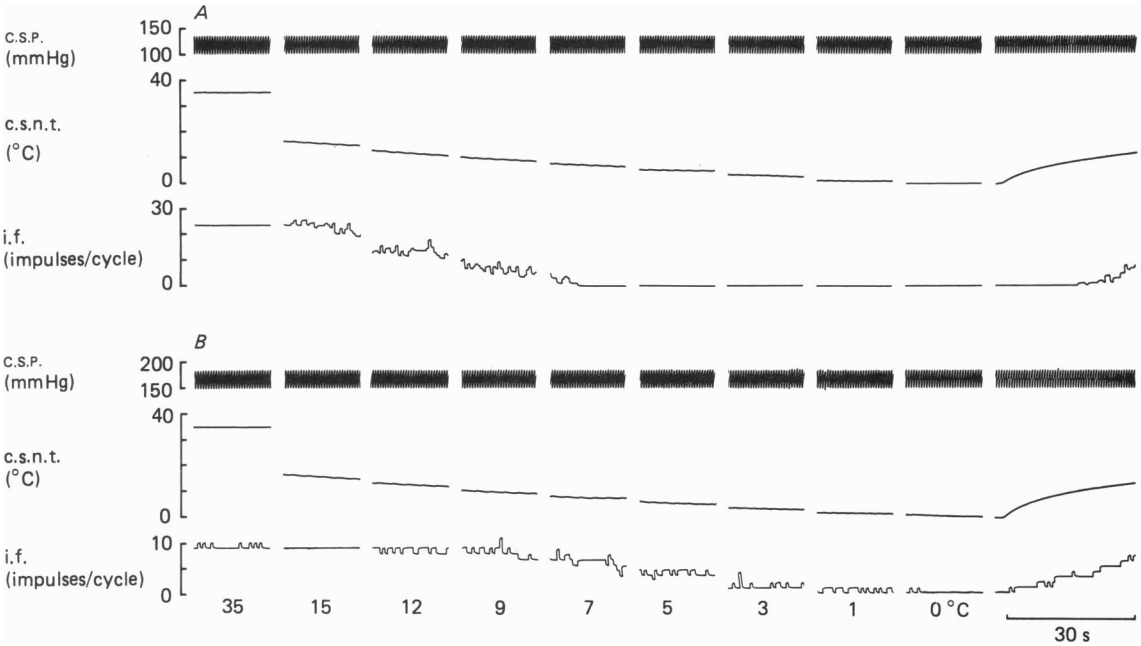

Fig. 9. Attenuation of impulse activity in baroreceptor fibres by progressive cooling of the carotid sinus nerve. *A*, A fibre baroreceptor; *B*, C fibre baroreceptor. C.S.P., carotid sinus pressure; c.s.n.t., carotid sinus nerve temperature; i.f., impulse frequency of baroreceptor (impulses/cycle) counted by rate-meter. Note that conduction in the A fibre is blocked at 7 °C and conduction in the C fibre at 0 °C.

the two groups of baroreceptor fibres differed markedly, C fibres being significantly more resistant to cooling (Fig. 10).

At 37 °C, the average impulse activity recorded in baroreceptor A fibres was 3–4 times that in C fibres. Nevertheless, the proportionate decrease in firing across the cooled region of nerve was greater in A fibres than in C fibres, and when the nerve was cooled to 7 °C the average conducted activity in C fibres exceeded that in A fibres. At 7 °C, more than 40% of A fibres were blocked and activity crossing the cooled region of nerve averaged only 10% of that at 37 °C. By contrast, at 7 °C all C fibres were still conducting, their activity averaging more than 60% of that at 37 °C (Fig. 10*B*).

Cooling the sinus nerve to 5 °C virtually abolished afferent input in baroreceptor A fibres, but still left C fibres with an appreciable input – all C fibres were active, their impulse frequency averaging 45% of control. Impulse transmission persisted in

C fibres to very low temperatures, indeed a majority of C fibres still transmitted impulses at 3 °C, and 25% continued to do so at 0 °C, at a frequency of 0·5–2·0 impulses/s. All C fibres were blocked at −1·5 °C.

We also examined the effects of cooling the carotid sinus nerve on conduction in baroreceptor fibres at various levels of carotid sinus pressure between 75 and 200

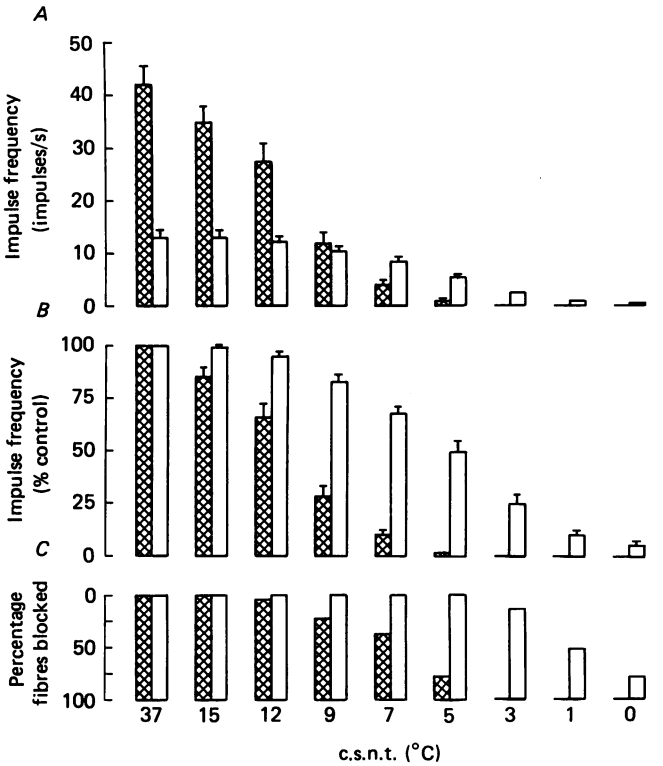

Fig. 10. Progressive blockade of conduction in baroreceptor fibres by cooling the carotid sinus nerve. Observations on twenty-seven A fibres (hatched blocks) and thirty-seven C fibres (open blocks); data are means ± S.E.M. *A*, effect of cooling on impulse frequency recorded central to the cooling platform. *B*, impulse frequency expressed as a percentage of the control at 37 °C. *C*, percentage of fibres in which conduction was blocked completely. c.s.n.t., carotid sinus nerve temperature. Carotid sinus pressure was kept constant at a mean pressure corresponding to the mid-point of the average stimulus–response curve (120 mmHg for A fibres and *ca.* 160 mmHg for C fibres).

mmHg (Fig. 11). Although cooling the sinus nerve to 7 °C did not block conduction in A fibres, the attenuation of conduction was such that the average conducted impulse frequency in baroreceptor A fibres at a carotid sinus pressure of 200 mmHg was no greater than that at a pressure of 75 mmHg (Fig. 11*A*). By contrast, at 7 °C baroreceptor C fibres still provided a signal proportional to sinus pressure (Fig. 11*B*).

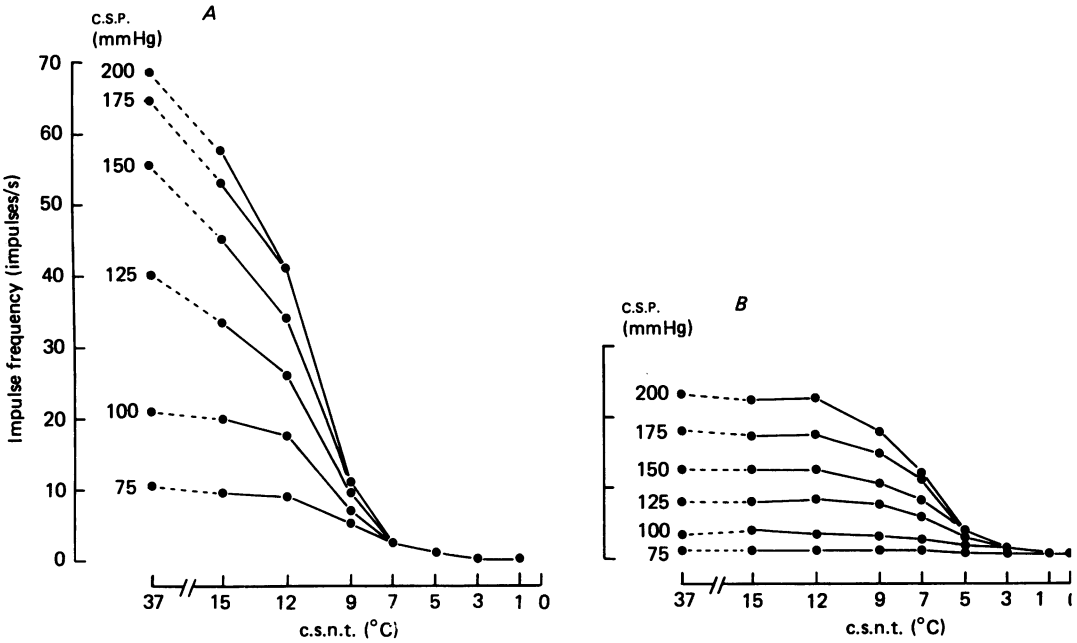

Fig. 11. Progressive cold blockade of baroreceptor A and C fibres at different levels of carotid sinus pressure. *A*, average results in eight A fibres; *B*, average results in eight C fibres. Impulse frequency recorded central to the cooling platform; c.s.n.t., carotid sinus nerve temperature; C.S.P., carotid sinus pressure. Note that at 7 °C the impulse frequency conducted across the cooling platform in A fibres was not related to sinus pressure, whereas that in C fibres still showed an obvious pressure–response relationship. In *B*, the activity recorded in C fibres at a sinus pressure of 75 mmHg was irregular and occurred below the pulsatile firing threshold.

DISCUSSION

Identification of A and C fibre baroreceptors

A and C fibre baroreceptors had very different stimulus–response characteristics, C fibre baroreceptors having pressure thresholds much higher, and sensitivities and maximal firing frequencies much lower, than those of their myelinated counterparts. We agree with Yao & Thoren (1983) who measured conduction velocities in their afferent studies in rabbits and found that A and C fibre baroreceptors could be identified by their characteristic patterns of response alone. It was our experience that having identified a baroreceptor by its pulsatile discharge we could assign it provisionally to one or other group on the basis of its firing at the set-point pressure of 100 mmHg. The A fibre baroreceptors fired briskly at the set-point, with frequencies many times those of the most active C fibres, indeed many C fibres were silent at the set-point. We confirmed our provisional identification of A and C fibre baroreceptors by measuring fibre conduction velocity or blocking temperature (see below), or both.

Our C fibre baroreceptors probably correspond to the carotid sinus baroreceptors with small spikes described by Landgren (1952*a*) in cats and Wiemer & Kiwull (1967)

in rabbits. However, we found that spike height could be an unreliable guide to fibre identity, for potentials in a C fibre were sometimes larger than those in an A fibre in the same nerve strand.

Stimulus–response characteristics of A and C fibre baroreceptors

Although the stimulus–response characteristics of our A fibre baroreceptors were generally similar to those of carotid baroreceptors previously described in dogs, comparisons are difficult because the experimental techniques differed. For example, generally higher pressure thresholds were observed when the carotid sinus was distended with a non-pulsatile pressure (Sleight, Robinson, Brooks & Rees, 1977; Gilmore & Tomomatsu, 1984; Heesch, Thames & Abboud, 1984) than when it was distended with a pulsatile one (Pelletier, Clement & Shepherd, 1972, present results). Furthermore, though previous investigators assumed that the afferent properties they described were those of A fibre baroreceptors, no steps were taken to distinguish A and C fibres.

Both A and C fibre baroreceptors displayed directional sensitivity of hysteresis, so that baroreceptor thresholds were significantly lower when pressure was increasing than when it was decreasing. Baroreceptors with A fibres, like those in the aorta in rabbits (Angell James, 1971) and dogs (Coleridge *et al.* 1981; Coleridge, Coleridge, Poore, Roberts & Schultz, 1984), showed hysteresis both above and below the baseline pressure of 100 mmHg; consequently the steep part of their response curve straddled the set-point, firing decreasing markedly for relatively small reductions in pressure below the set-point and increasing markedly for relatively small increases above it (Figs 4 and 6). Because C fibre baroreceptors were largely inactive below the set-point, hysteresis had virtually no effect on the steepness of their response curve.

A and C fibre baroreceptors differed in another respect. Although activity increased with sinus pressure in both A and C fibres, the augmented discharge in A fibres resulted from increases in both burst frequency and burst duration whereas that in C fibres was due mainly to an increase in burst duration (Table 1). The generally unchanging burst frequency of C fibre baroreceptors suggests that they have over-damped frequency–response characteristics, a phenomenon well described for aortic C fibre baroreceptors in rats (Brown, Saum & Yasui, 1978), and raises the possibility that large increases in heart rate may act to limit input from C fibre baroreceptors.

The stimulus–response characteristics of C fibre baroreceptors in the carotid sinus of dogs were generally similar to those of C fibre baroreceptors in the carotid sinus in cats (Fidone & Sato, 1969) and rabbits (Yao & Thoren, 1983) and in the aortic arch and brachiocephalic artery in rabbits (Thoren & Jones, 1977; Yao & Thoren, 1983), rats (Thoren, Saum & Brown, 1977; Brown *et al.* 1978) and dogs (Kaufman, Baker, Coleridge & Coleridge, 1978). However, C fibre baroreceptors in the carotid sinus of rabbits and dogs appear to differ in some respects. In rabbits, thresholds of A and C fibre baroreceptors overlapped, the average threshold of C fibres (92 mmHg) being 35 mmHg higher than that of A fibres (Yao & Thoren, 1983). In dogs, there was no overlap, and the average threshold of C fibres (106 mmHg) exceeded that of A fibres by about 50 mmHg. Possibly the relatively higher threshold of C fibres in dogs

reflects a true species difference. On the other hand, pulse pressure was kept constant in our experiments, but appeared to increase considerably in at least some of Yao & Thoren's experiments as mean pressure was raised. Since pulse pressure is an important determinant of baroreceptor threshold, such an increase could have served to decrease threshold.

C fibre baroreceptors in rabbits and dogs also differed in their effective firing range. In rabbits, the pressure range over which C fibres provided a signal proportional to blood pressure was only half that for A fibres; C fibres not only had a higher threshold than A fibres but their firing reached a plateau at 140 mmHg, whereas that in A fibres still increased when pressure was raised to 150 mmHg (Yao & Thoren, 1983). In dogs, C fibre baroreceptors had a much wider pressure range, which extended above that for A fibres. At a sinus pressure of 180 mmHg the impulse traffic in C fibres was only 73% of maximal, whereas that in A fibres had reached 97%; even when sinus pressure was raised from 200 to 220 mmHg C fibre activity still increased (by 7·5%), whereas that in A fibres was virtually unaltered.

The irregularity of the pulsatile discharge of C fibre baroreceptors prompted Yao & Thoren (1983) to suggest that although these afferents could monitor changes in mean pressure they were not suited to signal changes in pulsatile pressure. We found, however, that the variability of C fibre discharge decreased appreciably at higher pressures (Table 2) when C fibre input is probably of most significance. The greater variability of firing in C fibres than in A fibres was not due to the lower discharge frequency in the former, because it was still apparent when the two were compared at carotid sinus pressures evoking approximately the same level of activity (Table 2). It is likely that, as Brown (1980) suggests, the difference in the regularity of discharge reflects a basic difference in the coupling between receptor and vessel wall.

The different afferent properties of A and C fibre baroreceptors are usually explained in terms of the relationship between the baroreceptor terminals and the structural elements of the vessel wall. Thus, Landgren (1952*b*) predicted on the basis of electrophysiological studies that baroreceptors with large spikes (i.e. A fibres) were in parallel with smooth muscle elements, whereas those with small spikes (i.e. C fibres) were in series. This prediction appeared to be supported by the morphological studies of Rees (1967) who interpreted his results as showing that baroreceptors in parallel with smooth muscle are related to elastin and stretch more readily and have a lower threshold than those in series, which are related to collagen. However, the evidence is not conclusive, and, although the connections of the complex unencapsulated endings of baroreceptors with myelinated fibres have been well described (Bock & Gorgas, 1976; Krauhs, 1979), precise information about those of the simpler endings of baroreceptors with non-myelinated fibres is lacking (Krauhs, 1979). Even so, the hypothesis that baroreceptors with myelinated fibres are tightly coupled to the elements of the vessel wall and have a lower threshold than the more loosely coupled baroreceptors with non-myelinated fibre (Brown *et al.* 1978) remains an attractive one.

It is well known that some baroreceptors do not remain silent when pressure is reduced below the pulsatile firing threshold but begin to fire irregularly (Landgren, 1952*a*; Green, 1967; Coleridge *et al.* 1981). Our results indicate that baroreceptors

with C fibres are particularly prone to display this paradoxical behaviour. Paradoxical baroreceptor firing has been attributed to abnormal wall stress at low intrasinusal pressure (Landgren, 1952*a*; Green, 1967). However, it is not clear why C fibre endings should be more susceptible to the deformation resulting from low intrasinusal pressure; indeed in our experiments paradoxical firing occurred in C fibres at pressures above the firing threshold of A fibres.

Attenuation of baroreceptor input by cooling

Previous investigators who compared the effects of cooling on conduction in myelinated and non-myelinated axons usually stimulated the nerve electrically, beginning with trains of stimuli delivered at the maximal frequency the individual axon could follow (up to 1000 Hz for myelinated axons and 300 Hz for non-myelinated ones) and continuing with progressively lower frequencies as the nerve was cooled (Paintal, 1965, 1967; Franz & Iggo, 1968; Linden, Mary & Weatherill, 1981). In our experiments, baroreceptors were stimulated by pulsatile distension of the carotid sinus and fired with impulse frequencies and patterns of discharge comparable to those evoked naturally. Hence our results are readily applicable to reflex studies in which graded cooling is used to compare the functional roles of A and C fibre baroreceptors stimulated by a pulsatile pressure (Schultz, Pisarri, Coleridge & Coleridge, 1984).

Our results are in general agreement with previous observations: cooling progressively attenuated impulse conduction in both A and C fibres, the former being more susceptible to cooling. The average blocking temperature (6·8 °C) of A fibres in our experiments was comparable to that reported previously (7·6 °C, Paintal, 1965; 6·5 °C, Paintal, 1967; 7·2 °C, Franz & Iggo, 1968; 8 °C, Linden *et al.* 1981), whereas the average blocking temperature (1·0 °C) of our C fibres was lower (4·3 °C, Paintal, 1967; 2·7 °C, Franz & Iggo, 1968; 3·7 °C, Linden *et al.* 1981). However, the low blocking temperature of our C fibres was not necessarily in conflict with the earlier findings, for Franz & Iggo (1968) reported a relatively large proportion of C fibres with blocking temperatures between 0·8 and 0·3 °C and speculated that the blocking temperature of 'undisturbed non-myelinated axons' was likely to be close to 0 °C.

The effects of cooling are frequency dependent, the higher the firing frequency the greater the attenuation, but the relative resistance of C fibres to cooling was not due to their lower discharge frequency. The average impulse frequency in C fibres at a sinus pressure of 200 mmHg was more than twice that in A fibres at a pressure of 75 mmHg, yet conduction in the former survived cooling to a lower temperature. The mode of conduction is probably the crucial factor, the saltatory conduction in myelinated fibres rendering them more susceptible to cooling (Paintal, 1967).

We also cooled the carotid sinus nerve in order to determine whether baroreceptor C fibres still provided the medullary centres with an afferent input proportional to carotid sinus pressure after baroreceptor input in A fibres had been eliminated. Although conduction in some A fibres persisted at low temperatures, our results indicate that it is not necessary to block all baroreceptor A fibres in order to examine the reflex role of C fibre baroreceptors, but only to cool the nerve until A fibre input no longer varies with carotid sinus pressure. This can be achieved by cooling to 7 °C, at which temperature an increase in sinus pressure from 75 to 200 mmHg will evoke

a tenfold increase in C fibre input but have no effect on A fibre input (Fig. 11). Consequently any baroreflex effects evoked at 7 °C will be of C fibre origin. However, the total contribution of C fibre baroreceptors to baroreflexes will not be represented fully by the reflex effects that survive cooling to 7 °C because the functional blockade of baroreceptor A fibres at 7 °C will be accompanied by a 33% reduction in the input in baroreceptor C fibres, resulting presumably in a corresponding attenuation of reflex potency.

Functional role of A and C fibre baroreceptors

Since A fibre baroreceptors are active at the normal arterial pressure set-point, they are able to buffer both increases and decreases in arterial blood pressure. C fibre baroreceptors, on the other hand, are probably of little importance in cardiovascular regulation at normal arterial pressure but are increasingly brought into play as pressure exceeds the set-point. Moreover, since C fibre baroreceptors appear to outnumber those with A fibres (Rees, 1967; Fidone & Sato, 1969; present results), since they continue to be recruited at sinus pressures well above the set-point, and since their firing continues to increase with pressure after that in A fibres has reached a plateau, they are likely to provide a progressively larger share of baroreceptor inhibitory input to the vasomotor centres as blood pressure increases. The notion that the inhibitory influence of C fibre baroreceptors may even surpass that of A fibre baroreceptors as blood pressure increases is supported by the recent observation in dogs that carotid C fibre baroreceptors, unlike their myelinated counterparts, do not undergo hypertensive resetting (Schultz, Pisarri, Coleridge & Coleridge, 1985).

Reflex studies provide good evidence that C fibre baroreceptors have an inhibitory influence on the vasomotor centres. Thus recruitment of baroreceptor C fibres by electrical stimulation of the aortic and carotid sinus nerves evokes powerful depressor effects that differ in certain respects from those evoked when only baroreceptors with myelinated fibres are stimulated (Douglas & Ritchie, 1956; Douglas, Ritchie & Schaumann, 1956; Kardon, Peterson & Bishop, 1975). The inhibitory influence of C fibre baroreceptors on sympathetic outflow to the heart and hindlimb vascular bed was recently demonstrated by increasing pressure in the vascularly isolated carotid sinus after conduction in baroreceptor A fibres had been blocked by cooling the sinus nerve to 7 °C (Schultz *et al.* 1984).

Irregularly firing fibres

We encountered a number of C fibres that were stimulated by increasing carotid sinus pressure but responded with an irregular rather than a pulsatile discharge. Their threshold was higher than that of the C fibre baroreceptors, and their sensitivity and maximal firing frequency lower. We do not think that they should be equated with the irregular firing C fibre baroreceptors described by previous investigators. The aortic C fibres studied by Thoren *et al.* (1977) in rats showed a pronounced variation in instantaneous frequency when the aorta was distended with a steady pressure, but their discharge had an obvious pulse-related modulation in the few instances in which pressure was pulsatile. Similarly, the carotid sinus C fibres, described by Yao & Thoren (1983) in rabbits, fired irregularly in the sense that impulse frequency did not always follow pressure faithfully; nevertheless firing

always had a cardiac rhythm. Our irregularly firing fibres never had an obvious pulse-related modulation, even when carotid sinus pressure was pulsatile around a mean of 220 mmHg.

We do not think that these irregularly firing endings should be regarded as baroreceptors in the conventional sense. They appear to have more in common with certain slowly conducting vagal fibres that arise from afferent endings in the heart and adjacent great vessels (Coleridge, Coleridge & Kidd, 1964; Coleridge, Coleridge, Dangel, Kidd, Luck & Sleight, 1973; Kaufman, Baker, Coleridge & Coleridge, 1980). The vagal endings have a high pressure threshold and their discharge is irregular, not pulse related. They are stimulated by chemicals, including bradykinin and the prostaglandins, that have no direct effect on conventional baroreceptors or cardiac mechanoreceptors (Coleridge *et al.* 1964, 1973; Kaufman *et al.* 1980; Roberts, Coleridge, Coleridge, Kaufman & Baker, 1980). Whether the irregularly firing endings in the carotid sinus are also susceptible to these chemicals remains to be determined. It is possible that they contribute to the C fibre component of carotid baroreflexes. However, since they represented only 17% of the pressure-sensitive C fibres identified in the sinus nerve, and since their average response to a given increase in pressure was less than half that of the C fibre baroreceptors, any contribution to carotid baroreflexes is likely to be small.

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