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THE CENTRAL PROJECTIONS OF CAROTID BARORECEPTORS AND CHEMORECEPTORS IN THE CAT: A NEUROPHYSIOLOGICAL STUDY

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SUMMARY

1. The medullary projections of afferent neurones with cell bodies in the petrosal ganglion have been investigated using an antidromic mapping technique.

2. Of the ninety-three units studied, fifty-eight were shown to have patterns of discharge indicating that they were baroreceptors and thirty-five showed responses to stimuli indicating that they were arterial chemoreceptors.

3. Twelve baroreceptor and thirteen chemoreceptor afferents had sufficiently stable unitary discharges to permit a detailed estimation of some of their central projections using stimulation through monopolar tungsten micro-electrodes to evoke antidromic spikes. In order to estimate their pattern of projection, depth–threshold contours for each penetration through the dorsomedial medulla and the values of antidromic latency were considered.

4. Baroreceptor afferent fibres with myelinated (six units) and non-myelinated (six units) axons showed similar patterns of central projection. All could be activated from the ipsilateral nucleus of the tractus solitarius (n.t.s.), most often from its lateral divisions rostral to the obex. The dorsolateral and dorsomedial portions of the n.t.s. were most often innervated, with the commissural subnucleus receiving an innervation in seven of the twelve neurones studied. Stimulation of the ventrolateral subnucleus was effective in activating two afferent fibres whilst stimulation of the ventral subnucleus was effective in only one case.

5. All chemoreceptor afferent fibres had calculated conduction velocities less than 4 m/s and all were activated from the dorsomedial and medial subnuclei of the ipsilateral n.t.s. In twelve of the thirteen neurones investigated in detail there was evidence of an innervation of the commissural nucleus both at the level of the obex and behind it. In three cases this extended into the contralateral portion of the commissural nucleus. In four cases a sparse innervation of the lateral subnucleus, comprising its dorsolateral aspects, was seen.

6. The potential significance of these distinctive patterns of projection of arterial baroreceptors and chemoreceptors is discussed in relation to cardiovascular and respiratory control.

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INTRODUCTION

In previous reports from this Laboratory, we have described the brain-stem projections in both cat and rabbit of aortic baroreceptors (Donoghue, Garcia, Jordan & Spyer, 1982*a*) and lung stretch afferents (Donoghue, Garcia, Jordan & Spyer, 1982*b*) using an antidromic mapping technique (Lipski, 1981; Donoghue, Jordan & Spyer, 1983). This involved making extracellular recordings of the activity of vagal sensory neurones within the nodose ganglion and activating their afferent projections within the medulla oblongata by electrical stimulation with micro-electrodes.

In the cat, the aortic baroreceptors, which had been identified on the basis of their ongoing pattern of discharge, were shown to project to the ipsilateral medial or lateral subnuclei of the nucleus tractus solitarius (n.t.s.), or both, as well as innervating both ipsilateral and contralateral portions of the commissural subnucleus. The most marked innervation was, however, of the lateral portions of the n.t.s. Conversely, lung stretch afferents projected mainly to medially placed regions of the n.t.s.

The pattern of central projection of the baroreceptors of the carotid sinus and chemoreceptors of the carotid body remain to be identified within the n.t.s. (Spyer, 1981 for review). The comparative central projections of these and the receptors described above may provide an insight into the role of the different portions of the n.t.s. in cardiovascular and respiratory control. Accordingly, the present report will describe experiments in which the activity of both baroreceptor and chemoreceptor afferents have been recorded in the petrosal ganglion of the cat and the central projections of individual physiologically defined afferents have then been traced neurophysiologically. Preliminary reports of these studies have been published (Donoghue, Felder, Jordan & Spyer, 1982*a*; Donoghue *et al.* 1983).

METHODS

Experiments were carried out on twenty-eight adult cats (2·0–3·5 kg body weight). The animals were anaesthetized with sodium pentobarbitone (Sagatal, May & Baker Ltd, 40 mg/kg I.P.) or by α-chloralose (BDH, 70 mg/kg). In all animals, a femoral vein was cannulated for administration of supplemental anaesthetic and drugs. Arterial blood pressure was monitored continuously by a cannula in a femoral artery. Throughout the experiment supplementary doses of these anaesthetics were given, when necessary, to maintain a stable level of anaesthesia as judged from recordings of arterial blood pressure and heart rate. The trachea was intubated low in the neck and the animal artificially respired with air (Harvard Ventilator) to maintain end-tidal CO_2 at $4{\cdot}0 \pm 0{\cdot}5\%$ (P. K. Morgan 901 CO_2 analyser). Rectal temperature was maintained at $37{\cdot}5 \pm 0{\cdot}5$ °C with a heating blanket and feed-back control.

The carotid sinus nerve was isolated at its junction with the glossopharyngeal nerve by a lateral approach in the neck as described previously (Lipski, McAllen & Spyer, 1975). The animal was then placed prone in a stereotaxic head-holder (David Kopf Instruments) and the dorsal surface of the medulla exposed and prepared for stimulation (Jordan & Spyer, 1977). To approach the petrosal ganglion the muscles overlying the tympanic bulla were removed and the glossopharygeal nerve traced centrally till it was seen to pass into the skull. By carefully removing the bone surrounding the nerve the petrosal ganglion was exposed.

The exposed ganglion was initially embedded in agar but prior to recording a small hole was made to expose part of the ganglion. If necessary its connective sheath was separated. Before recording, the glossopharyngeal nerve was ligated distal to its junction with the sinus nerve. Extracellular unit activity was recorded from the ganglion using glass-coated tungsten micro-electrodes, or single-barrelled glass micro-electrodes filled with 2 M-NaCl. Extracellular unit activity was recorded

and amplified using conventional neurophysiological techniques, displayed on an oscilloscope (Tektronix 5000 series) and electrostatic recorder (Gould ES 1000), and stored on magnetic tape (Racal Store 7).

Ongoing activity of neurones recorded within the petrosal ganglion was analysed by constructing electrocardiogram (e.c.g.)-triggered histograms of activity using a minicomputer (Cambridge Electronic Design Ltd., Slam system). The activity was also investigated during alterations in arterial blood pressure produced by (i) controlled haemorrhage, (ii) re-infusion of blood or dextran–saline and (iii) I.V. injections of adrenaline. Alterations in discharge in relationship to arterial blood gas tension, as indicated by end-tidal CO_2, were investigated by (i) varying the rate and tidal volume of the artificial ventilation, (ii) adding a 5% CO_2/95% O_2 gas mixture to the inspired gas or (iii) occluding the carotid arteries below the carotid bifurcation. Using these tests in combination it was possible to identify neurones which had physiological properties indicative of either a baroreceptor or chemoreceptor function.

Following identification of a neurone the animal was paralysed with Flaxedil (gallamine triethiodide, initially 4 mg/kg I.V. with a maintenance dose of 1–4 mg/kg.h). Using a Digitimer and isolated stimulator, constant current cathodal pulses of up to 100 μA, 0·1–1·0 ms duration at frequencies of 0·5–200 Hz, were applied to the brain stem via monopolar tungsten micro-electrodes (impedances 20–60 kΩ measured at 1 kHz). The medulla was explored in a serial manner to determine sites from which the neurone could be activated antidromically by such electrical stimulation. The standard criteria of constant latency and collision with a spontaneous spike were taken as evidence of antidromic activation. For each penetration, during which a cell was antidromically activated, a plot of the threshold for activation against electrode depth was constructed using a constant stimulus pulse duration (usually 0·1 ms) and frequency (1·0 Hz.).

Histology

At the end of each experiment the brain was removed and fixed in 10% formol saline. Frozen sections 50 μm thick were cut and stained with Neutral Red. The path of the electrode tracts could then be determined microscopically. The exact locations of the sites of stimulation were then determined as has previously been described in full (Lipski *et al.* 1975) either by interpolation between two points in an electrode tract or by extrapolation from one marked point.

RESULTS

In recordings made from petrosal ganglia in twenty-eight cats, the activity of several hundred afferent neurones was recorded. Of these, ninety-three unit recordings were made for a sufficient time to enable a study to be made of their physiological properties. Fifty-eight units had patterns of discharge indicative of a baroreceptor function whilst thirty-five units showed responses suggesting a chemoreceptor function. Baroreceptor afferents were classified on the basis of (a) a pulse-modulated discharge, which (b) altered appropriately in relation to the level of mean arterial pressure and (c) was abolished reversibly by occluding the carotid artery beneath the ipsilateral carotid sinus for 2–3 s. These properties are illustrated for two individual afferents which subsequently proved to have myelinated and non-myelinated axons respectively (Figs. 1 and 2). For the purpose of the present report no quantitative evaluation has been made of their pattern of discharge with respect to any particular parameter of arterial blood pressure.

The thirty-five units which were classified as chemoreceptor afferents, presumably with endings in the carotid body, showed a distinctly different pattern of discharge. They exhibited an irregular discharge which was increased on occluding the carotid artery for 30–60 s, or by increasing arterial CO_2 tension (Fig. 3) as monitored by changes in end-tidal CO_2.

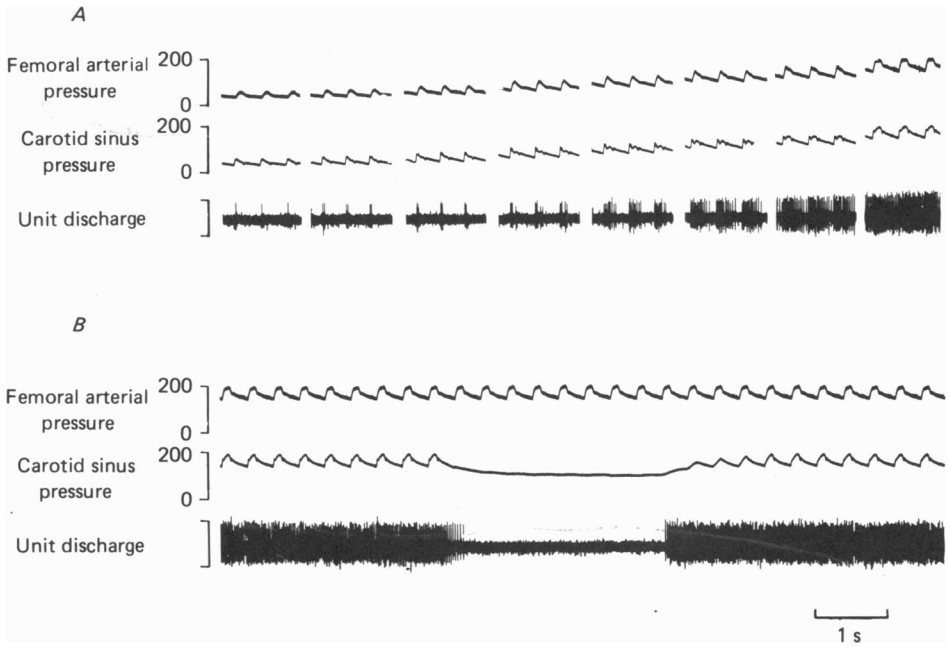

Fig. 1. From above, original records of femoral arterial pressure, external carotid arterial pressure and ongoing discharge of a carotid sinus baroreceptor afferent which was subsequently shown to have a myelinated axon (conduction velocity 7·5 m/s). *A*, the 4th column shows the resting situation, columns to the left were taken at periods during controlled haemorrhage, columns to the right after re-infusion of blood and extracellular fluid expansion with an intravenous infusion of dextran–saline. *B*, the influence of occluding the ipsilateral common carotid artery below the carotid sinus. This recording was made immediately after that illustrated in *A*. The period of occlusion is indicated by the static pressure trace from the carotid artery.

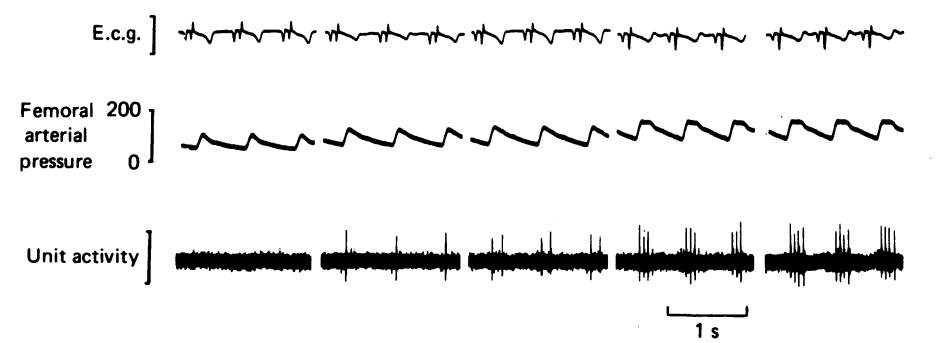

Fig. 2. From above, original records of electrocardiogram (e.c.g.), femoral arterial pressure and ongoing discharge of a carotid sinus baroreceptor afferent which was subsequently shown to have a non-myelinated axon (conduction velocity 0·8 m/s). The third column shows resting data, columns to the left were taken after controlled haemorrhage and those to the right after re-infusion of blood and a supplementary infusion of isotonic saline.

From these ninety-three neurones, fourteen baroreceptor and fifteen chemoreceptor afferents were recorded that had a stable unitary potential for sufficient time to enable their central projections to the medulla to be assessed using microstimulation through monopolar tungsten micro-electrodes. Detailed maps of medullary projections were obtained from twelve baroreceptors and thirteen chemoreceptors which will be reported separately.

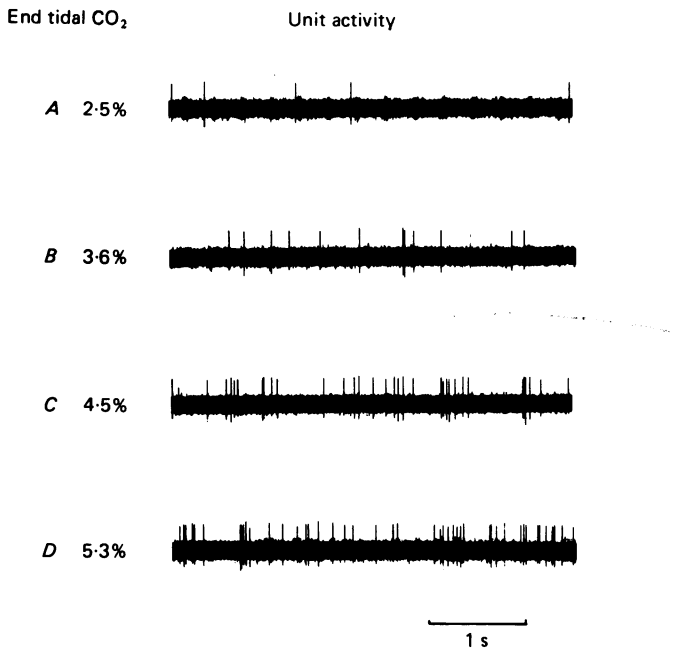

Fig. 3. Artificial ventilation. Recordings of the ongoing activity of a chemoreceptor afferent, which was subsequently shown to have a non-myelinated axon (conduction velocity 1·25 m/s), at different levels of end-tidal CO_2. End-tidal CO_2 was adjusted from the resting state (*B*) by hyperventilating (*A*) and hypoventilating (*C* and *D*).

Projections of carotid baroreceptor afferents

The baroreceptor afferents which were studied in detail (twelve afferents) had axonal conduction velocities in a range of 0·8–10 m/s calculated with reference to a conduction distance of 15 mm, extending from the petrosal ganglion to the tractus solitarius at a point 2 mm rostral to the obex and the measured latency of the antidromic response (range 1·5–25 ms) (Fig. 4*A*). Such values coincided closely with those calculated with respect to two points at different levels in the tractus solitarius (variation $< 5\%$). Considerable increases in latency over short distances within the medulla indicated stimulation at sites which we consider to correspond to areas of branching or termination of individual neurones (Donoghue *et al.* 1982*a*) (Figs. 5*B* and 6*B*). By constructing families of depth–threshold contours for the many penetrations made through the dorsomedial medulla in each experiment and with reference also to negative penetrations (i.e. from which no antidromic response was observed with the intensity of stimulation above 100 μA), it was possible to estimate

the pattern of projection (Donoghue *et al.* 1982*a*). The minimum current intensity to evoke an antidromic response varied with each unit and, most markedly, with respect to the particular stimulating electrode used, but was only greater than 10 μA in three cases (i.e. 20 μA for two units and 60 μA for one).

Typical depth–threshold curves and schematic maps of central projections are shown for two baroreceptor afferents, one with a myelinated axon (conduction

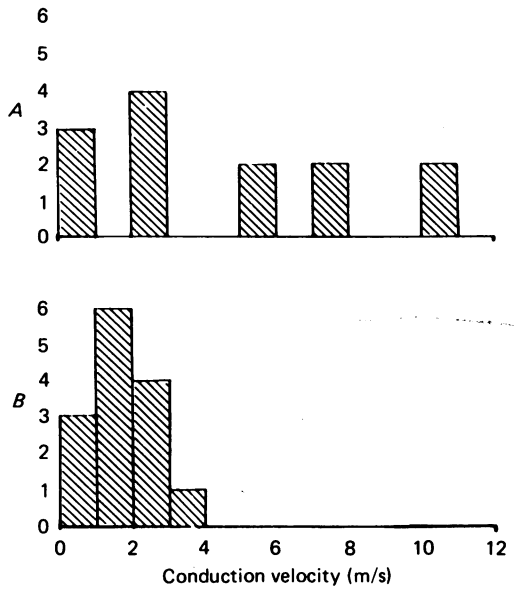

Fig. 4. Frequency histograms showing the range of calculated conduction velocities for baroreceptor (*A*) and chemoreceptor (*B*) afferents assuming a conduction distance of 15 mm from the petrosal ganglion to the ipsilateral tractus solitarius at a point 2 mm rostral to the obex.

velocity 7·0 m/s) (Fig. 5), the second with an axon with conduction velocity in the range of a C-fibre (conduction velocity 0·8 m/s) (Fig. 6). These both illustrate the typical pattern of projection. All baroreceptor afferents so far encountered have shown that projections to the n.t.s. at, and rostral to, the obex are restricted to the ipsilateral side. All had projections into the lateral subnucleus at levels from 1–2 mm rostral to obex, and to the medial subnucleus from 0–2 mm rostral to obex. The dorsolateral and dorsomedial portions of the nucleus were most often innervated whilst the ventrolateral subnucleus received an innervation in only two out of twelve cases and the ventral subnucleus only once. The commissural nucleus received an innervation in seven out of the twelve neurones studied. Only six penetrations extending beyond the borders of the n.t.s. contained points from which afferents were excited antidromically and these were all within 0·3 mm of the nucleus.

An attempt has been made to assess whether there is a difference in the pattern of projection of afferents with axonal conduction velocities below and above 3 m/s. There appears to be no consistent difference, both groups projected to the same areas

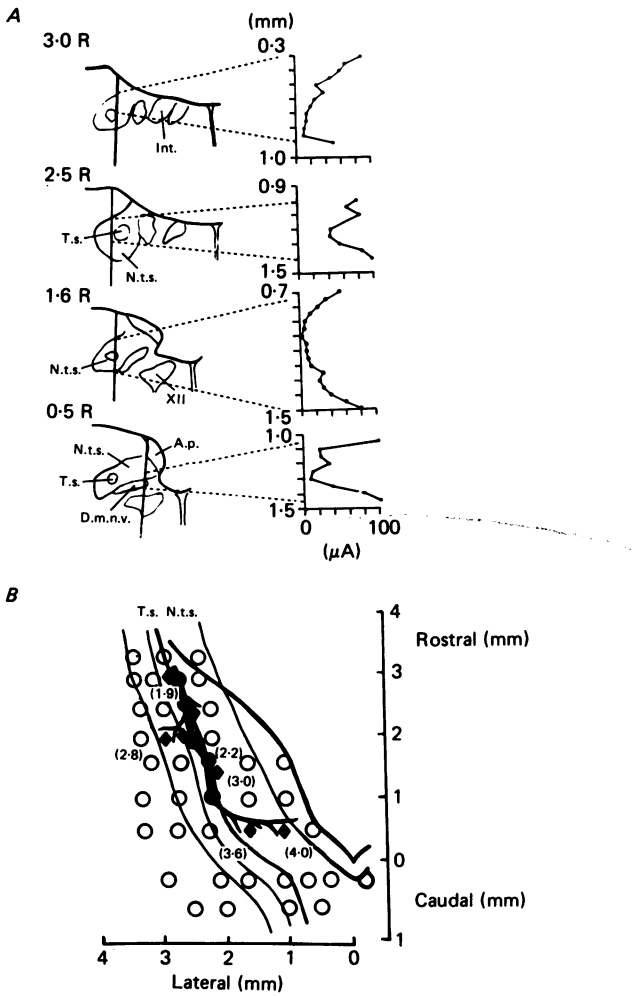

Fig. 5. Myelinated baroreceptor afferent (conduction velocity 7·0 m/s). *A*, cross-sections of the dorsomedial region of the medulla oblongata. The thick vertical lines each represent a stimulating electrode position. On the right are shown the depth–threshold profiles corresponding to these penetrations. *B*, a schematic view of the dorsal surface of the medulla oblongata showing the fourth ventricle. Superimposed on this is the medial and lateral extent of the tractus solitarius and its nucleus. Scales indicate distances (in mm) rostral (R), caudal (C), and lateral to the obex (O). Sites of stimulating electrode penetrations are indicated classed according to the type of depth–threshold profile obtained, i.e. point (●), field (◆) or no response (○). Figures in parentheses indicate the antidromic latency. A possible course of the main axon is shown by the thick line connecting point types, and regions of branching or termination by the thin lines. Abbreviations: area postrema (a.p.), dorsal motor nucleus of vagus (d.m.n.v.), nucleus commissuralis (n.comm.), tractus solitarius (t.s.), nucleus tractus solitarius (n.t.s.), nucleus intercalatus (int.), central canal (c.c.), hypoglossal nucleus (XII) and fourth ventricle (IV).

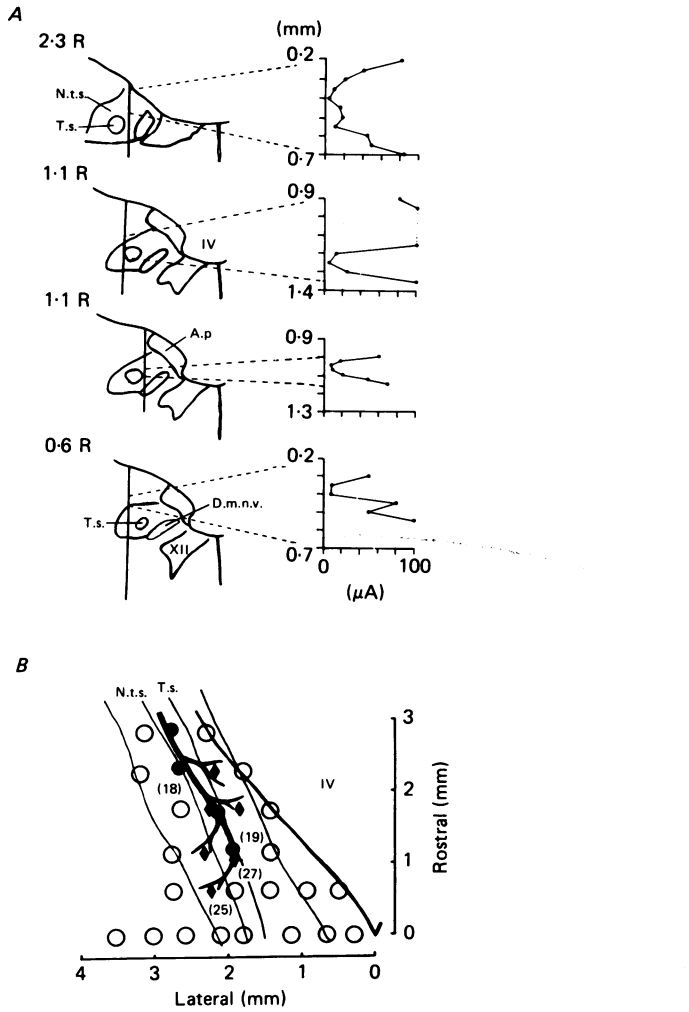

Fig. 6. Non-myelinated baroreceptor afferent (conduction velocity 0·8 m/s). *A*, penetrations and depth–threshold profiles. *B*, schematic map of full projections. Form of Figure and abbreviations as for Fig. 5.

of the n.t.s. Also, stimulation of one subnucleus was no more likely to activate one group of afferents than the other group.

The projection of carotid chemoreceptor afferents

From a total of thirty-five arterial chemoreceptor afferents, fifteen were studied sufficiently to show a projection to the n.t.s. Of these, thirteen were held for a sufficient length of time to indicate their pattern of central projection.

The calculated conduction velocity of their centrally projecting axon was 0·6–3·5 m/s (latency 3·6–24·0 ms) taking their projection to a point in the tractus solitarius 2 mm rostral to the obex as for baroreceptor afferents. The distribution of conduction velocities is illustrated in Fig. 4*B*. None had a significantly myelinated axon, in contrast to data relating to baroreceptor afferents (Fig. 4*A*).

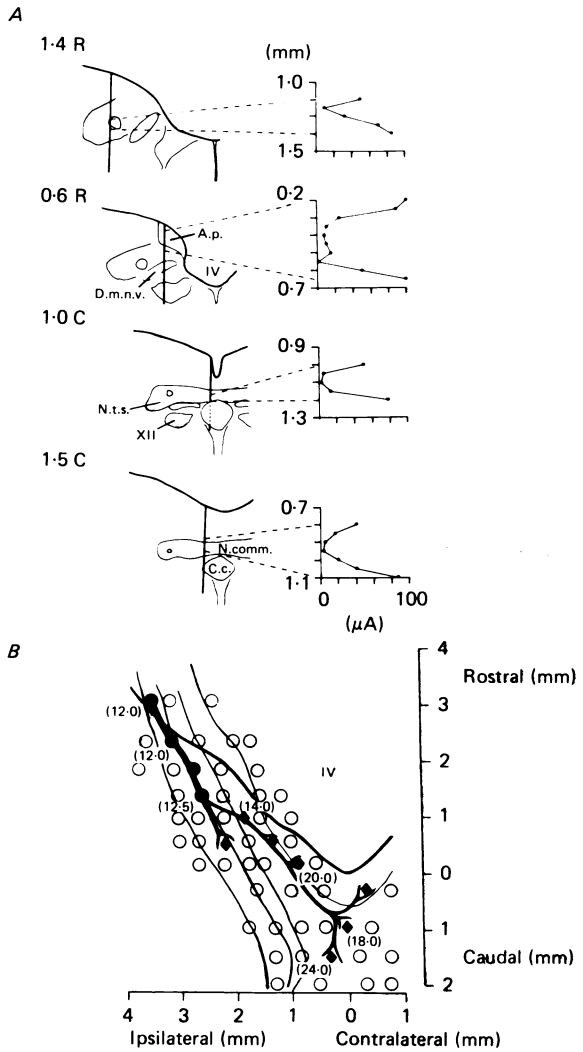

Fig. 7. Non-myelinated chemoreceptor afferent (conduction velocity 1·2 m/s). *A*, penetrations and depth–threshold profiles. *B*, schematic map of full projections. Form of Figure and abbreviations as for Fig. 5.

As for baroreceptor afferents, inferences about projections were made from data obtained by plotting depth–threshold contours (Fig. 7) together with estimates of the latency of evoked responses. Latencies of responses can be expected to increase greatly over short distances in regions of branching and terminal arborization (Donoghue *et al.* 1982*a*). These afferents were excited antidromically on intramedullary stimulation with minimum currents of < 2–$15\ \mu$A (mean $6{\cdot}2\ \mu$A; $n = 13$). In each case, the main axon appeared to descend rostro-caudally through the tractus solitarius whilst areas of branching and termination were identified in the dorsomedial and medial subnuclei of the n.t.s. in every case. In twelve of the thirteen neurones

studied in detail, the commissural nucleus at the level of, and caudal to, the obex received a projection from chemoreceptors; in three neurones this extended into the commissural nucleus on the contralateral side of the medulla. In addition, penetrations passing through the area postrema often evoked antidromic responses (see Fig. 7). For two afferents which were only partially mapped the medial subnucleus just rostral to the obex was innervated, and in one case, this extended into the ipsilateral commissural nucleus, at, and caudal to the obex.

Sparse lateral projections were observed for four afferents. These were most obvious in the dorsolateral region of the n.t.s. On no occasion was stimulation within the ventrolateral, or ventral subnucleus effective in evoking antidromic responses even at intensities of, or greater than, 100 μA.

DISCUSSION

This report details the extent of the separate projections into the central nervous system of individual carotid sinus baroreceptors and carotid body chemoreceptors. To the best of our knowledge, similar data are not available elsewhere since this is the first demonstration of the use of the antidromic mapping technique for these individual afferents. Previous conclusions on the central projections of sinus nerve afferents have relied on the transganglionic transport of the enzyme horseradish peroxidase (HRP) (Berger, 1979; Panneton & Loewy, 1980; Ciriello, Hrycyshyn & Calaresu, 1981; Davis & Kalia, 1981) but this has the disadvantage of failing to distinguish between chemoreceptor and baroreceptor projections. The extent of projections described in the present study, however, falls within the over-all limits set by the results of the HRP transport studies and those revealed by neurophysiological studies on the whole sinus nerve during medullary stimulation (Jordan & Spyer, 1977).

The carotid baroreceptor afferents studied here have fallen into two distinct groups on the basis of the calculated conduction velocity of their central axon. One group has non-myelinated, the other small myelinated axons but their patterns of central projection, as revealed using the antidromic mapping technique, are indistinguishable. Naturally, the limitations of this technique will not allow the fine details of their projections to be resolved (see Donoghue *et al.* 1982*a* for discussion) and micro-anatomical differences may well exist. It is interesting, however, that, with one exception, their patterns of projection are identical to those of aortic baroreceptors which were also studied in the cat (Donoghue *et al.* 1982*a*). The exception is that whilst myelinated aortic baroreceptors were shown to project to the contralateral commissural nucleus of the n.t.s. (Donoghue *et al.* 1982*a*) no such projection has been demonstrated for either myelinated or non-myelinated carotid baroreceptor afferents in the present study.

The overlap of termination of baroreceptors from different receptor regions has obvious implications for the role of the n.t.s. as an important centre for convergence and integration of cardiovascular afferent information. The distinct differences of this projection pattern to that of the termination of chemoreceptors is also striking. Whilst all baroreceptor afferents appear to show a preference for lateral aspects of the n.t.s., although not the ventral and ventrolateral portions, the chemoreceptors showed more

extensive terminations in medial regions of the n.t.s., and both ipsilateral and contralateral portions of the commissural portion of the n.t.s. In this the distribution of chemoreceptor projections is similar to that described previously for lung stretch afferents, although these were never seen to cross the mid line (Donoghue *et al.* 1982*b*). It should be noted that the population studied is small and may not be representative of the total population of baroreceptor and chemoreceptor afferents. Nevertheless, our findings strongly suggest that these two receptor groups innervate distinctly different subpopulations of n.t.s. neurones.

The observations in the present report are limited to what appear to be relatively slowly conducting afferents, particularly within the chemoreceptor population. Studies from other laboratories indicate that two-thirds of the fibres in the sinus nerve distal to the petrosal ganglion are non-myelinated, but of the myelinated fibres the majority are chemoreceptor in function (Heymans & Neil, 1958; Fidone & Sato, 1969). The distribution of fibre diameter with respect to the supraganglionic nerve is unknown but there is no evidence for a significant change. There is, however, evidence that some vagal afferents in the cat change their conduction velocity as they project centrally (Duclaux, Mei & Ranieri, 1976) and that central to the nodose ganglion the conduction velocity of the afferent fibres may be markedly reduced (Mei, 1970). This would indicate demyelination and it may be that chemoreceptor afferents in the sinus nerve show this more markedly than baroreceptor afferents. A sampling irregularity may account for our systematic failure to record from the cell bodies of myelinated chemoreceptor afferents. The technique is, however, adequate to record from neurones with myelinated axons in the nodose ganglion (Donoghue *et al.* 1982*a*, *b*) and for a number of carotid sinus baroreceptors in the present study. A detailed study is required to resolve this issue.

To consider the importance of the present observations in cardiovascular control one must take account of several previous studies. It has been proposed from a range of neurophysiological evidence that the dorso-medial n.t.s. is the site of the first synapse in the baroreceptor reflex (Seller & Illert, 1969). A recent intracellular study has claimed to have recorded from second-order neurones in the baroreceptor reflex on the basis of recording activity with pulse-modulated discharge in that same region (Czachurski, Lackner, Okert & Seller, 1982), but the use of pulse modulation as a means of defining 'cardiovascular' neurones has been criticized (Spyer, 1981). It should be noted that neurones with pulse-modulated discharge but having no inputs, excitatory or inhibitory, from either sinus or aortic nerves have been recorded in the dorsomedial n.t.s. (Donoghue, Felder, Jordan & Spyer, 1982*b*): this may indicate an input from cardiac vagal afferents. In contrast, the lateral divisions of the n.t.s. have been shown to contain neurones excited both by sinus nerve stimulation and specific stimulation of carotid sinus baroreceptors (Lipski, McAllen & Spyer, 1975; Lipski & Trzebski, 1975). Our present data would indicate that carotid baroreceptors (see above) and aortic baroreceptors (Donoghue *et al.* 1982*a*) project to both general areas of the n.t.s. implying that each region may contain second-order neurones.

With respect to the role of the nucleus in respiratory control, much is known of the role of respiratory neurones localized in the ventrolateral subnucleus in the generation of respiratory rhythm (Merrill, 1974; Richter, 1982). Whilst there is evidence indicating monosynaptic excitatory connexions between myelinated carotid

body chemoreceptors and inspiratory neurones of the n.t.s. on the basis of cross-correlation studies (Kirkwood, Nisimaru & Sears, 1979), our present study could be taken to indicate the absence of an anatomical substrate to mediate such influences. Our failure to antidromically activate chemoreceptor afferents from the ventrolateral n.t.s. might, therefore, seem unexpected. This apparent contradiction may, however, have a reasonable explanation. It stems from a belief that connexions between chemoreceptor afferents and inspiratory neurones occur at a somatic locus. If, however, the inspiratory neurones have profuse and widely distributed dendrites, axodendritic synapses distant from the soma could explain both the observations of Kirkwood *et al.* (1979) and our own data. Preliminary information indicates that the inspiratory neurones of the n.t.s. do have extensive dendritic arborizations passing far from the ventrolateral subnucleus into many other regions of the n.t.s., and beyond, as revealed by horseradish peroxidase labelling (D. W. Ricter, personal communication). This might also explain conveniently the failure of Donoghue *et al.* (1982*b*) to observe a significant innervation of the ventrolateral subnucleus by lung stretch afferents even though the Rβ group of n.t.s. inspiratory neurones are known to be excited monosynaptically by vagal lung stretch afferents (Richter, Camerer & Röhrig, 1979).

In conclusion, our data indicates that there are important differences in the regional innervation of the n.t.s. from arterial baroreceptors and chemoreceptors. These observations begin to assist a re-evaluation of the role of this nucleus in both cardiovascular and respiratory control and indicate the need for future combined neurophysiological and neuroanatomical studies.

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