CENTRAL NERVOUS INTEGRATION OF CARDIOVASCULAR CONTROL

By K. M. SPYER

Sophia Jex-Blake Professor of Physiology,
Department of Physiology, Royal Free Hospital School of Medicine,
Rowland Hill Street, London NW3 2PF

SUMMARY

In this account an attempt has been made to identify integrative interactions in the control of the cardiovascular system. Three main sites of such interaction have been considered, the nucleus of the tractus solitarius (NTS), the vagal preganglionic supply to the heart and sympathetic preganglionic neurones.

In the case of the NTS the extent and range of afferent inputs from cardiovascular and respiratory receptors have been reviewed. In addition the interactions of these inputs on the activity of NTS neurones have been indicated although the details are as yet vague. With respect to the baroreceptor reflex, it is clear that its relay through the NTS permits the action of intrinsic drives, such as inspiratory activity, and extrinsic drives, for example the defence reaction, to modify to a greater, or lesser, extent the efficacy of the reflex. In the case of respiratory activity, changes in transmission of baroreceptor activity through the NTS are minimal, since a baroreceptor effect can be shown to exert itself on CVM activity throughout the respiratory cycle under appropriate experimental conditions (McAllen & Spyer, 1978b). The effectiveness of this excitatory input is, however, 'gated' by a direct inspiratory control of CVM activity. This indicates an essentially integrative role of vagal preganglionic neurones. The role of inputs from the lungs themselves evoked during inspiration, which also contribute to the respiratory modifications of the baroreceptor reflex, in the control of CVM activity is as yet uncertain although evidence is accumulating to suggest that they act by a mechanism different from that of inspiratory drive.

The influence of the defence reaction on transmission through the NTS has yet to be fully documented, but it appears as if there may be the potential for a marked modification. However, it is now certain that an inhibitory control of CVM activity can be evoked from the hypothalamus which is independent of any modification of the baroreceptor input at that level of the NTS and acts rather through an inhibitory synaptic influence directly onto CVMs.

In much the same way the baroreceptor influence on sympathetic preganglionic neurones is determined by their excitability, an excitability which is dependent on the balance of activity in several bulbospinal inhibitory and excitatory pathways, as well as segmental inputs. The role, if any, of direct hypothalamo-spinal pathways and the nature and organization of the descending pathways involved in the defence reaction requires elucidation. Existing data, however, make it clear that the thoracic intermediolateral cell column is an important site in the integration of cardiovascular control.

INTRODUCTION

The role of the nervous system in the regulation of the cardiovascular system is a subject of considerable medical and scientific interest. In recent years much has been learnt concerning the effects of cardiovascular reflexes and the elaboration of central patterns of cardiovascular response appropriate to changing behaviour. Unfortunately, our knowledge of the neural mechanisms involved in the inter-actions between these different drives and control processes is limited. Indeed, for much of this century those investigating the nervous control of circulation have given little thought to site and manner of these interactions since it was believed that this regulation was the concern of a circumscribed medullary 'vasomotor' centre. This model, which was convenient for its simplicity, has proved to be irreconcilable with the results of recent neurophysiological and neuroanatomical studies, but has been sufficiently influential, if not stifling, as to prevent a general exposition of our present understanding of the nervous organization of cardiovascular control. Some notable attempts have been made to redress this deficit (Hilton, 1975; Wurster, 1977) and the present account is intended to continue this re-evaluation. It will attempt to identify certain of the sites of integration within the neuraxis, concentrating on the processing and modifications in performance of the baroreceptor reflex (Spyer, 1981).

The role of the autonomic preganglionic neurones in the integration of control of the heart and circulation will receive particular attention in this account. An attempt will also be made to establish how the main medullary sensory nucleus receiving information from peripheral cardiovascular and respiratory receptors, the nucleus of the tractus solitarius (NTS), functions in elaborating outputs that regulate cardiovascular activity.

I. THE AFFERENT INPUT TO THE NTS

The NTS receives a marked afferent input from a range of receptors whose activity influences both the cardiovascular and respiratory systems. Since there is a close functional relationship between the respiratory and cardiovascular systems, which has been the subject of a recent review (Koepchen, Hilton & Trzebski, 1980), all these inputs may ultimately influence heart rate and blood pressure. At present the organization of the baroreceptor, chemoreceptor and lung stretch receptor inputs to the NTS are best understood and particular emphasis in the present account will be laid on the first of these. The question of the extent and organization of the baroreceptor input to the NTS has been reviewed in detail elsewhere (Spyer, 1981) and it is probably sufficient in this account to refer only to the major contributions and, in particular, to details of the most recent investigations.

Using the anterograde and transganglionic transport of the enzyme horseradish peroxidase (HRP), the central projections of sinus (SN) and aortic (AN) nerves, which in most species contain both baroreceptor and chemoreceptor afferents, have been illustrated (Berger, 1979, 1980; Panneton & Loewy, 1980; Wallach & Loewy, 1980; Ciriello & Calaresu, 1981; Ciriello, Hrycyshyn & Calaresu, 1981; Davies & Kalia, 1981). Figure 1, taken from the study of Ciriello *et al.* (1981), illustrates the
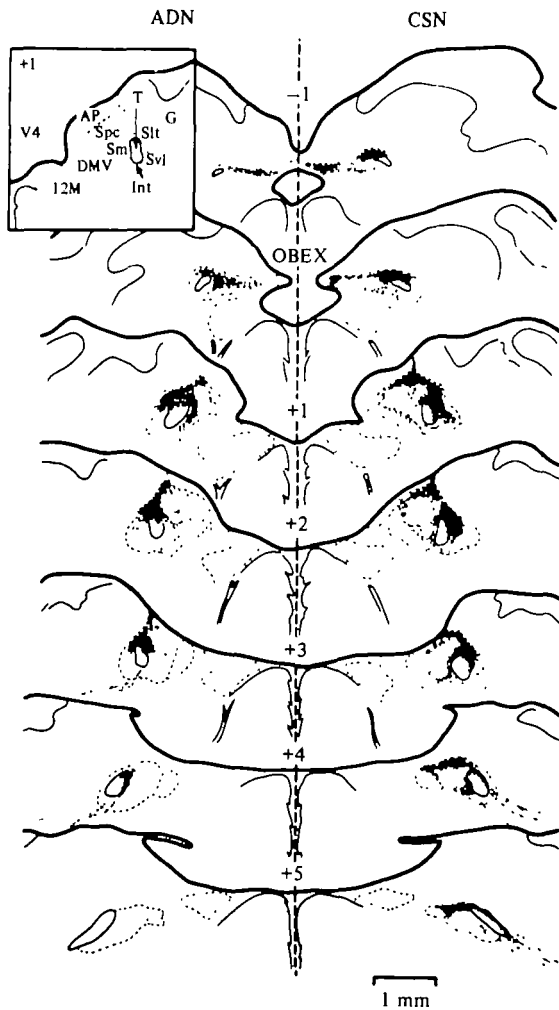
Fig. 1. Representative transverse sections of the dorsal medulla of the cat at intervals of 1 mm (from 1 mm caudal to 5 mm rostral to obex) showing the distribution of labelling following application of horseradish peroxidase (HRP) to the left aortic depressor nerve (ADN) and right carotid sinus nerve (CSN). Stippling indicates the presence of HRP reaction product. Box in upper left hand corner shows transverse section through region of the nucleus of the solitary tract. 12M, Hypoglossal nucleus; AP, area postrema; DMV, dorsal motor nucleus of the vagus; G, nucleus gracilis; Int, intermediate solitary nucleus; Slt, lateral solitary nucleus; Sm, medial solitary nucleus; Spc, parvocellular solitary nucleus; Svl, ventrolateral solitary nucleus; V4, fourth ventricle; T, solitary tract. (Ciriello & Calaresu, 1981.)

distribution of SN and AN afferents and their terminals within the NTS of the cat, as shown, using this technique. As a generalization it would seem that all the major subnuclei of this complex receive some innervation but the quantitative aspects of the distribution appear to differ depending on the particular research group involved in the study. Although the medial solitary nucleus, commissural and lateral solitary nucleus appear to be densely innervated (Berger, 1979, 1980; Ciriello & Calaresu, 1981; Ciriello et al. 1981), the ventrolateral appears only weakly but

distinctly innervated (Davies & Kalia, 1981; Ciriello & Calaresu, 1981). These observations do not, however, resolve whether the dorsomedial aspect of the nucleus represents a 'cardiovascular' nucleus (Seller & Illert, 1969) and the ventrolateral a 'respiratory' nucleus (Baumgarten & Kanzow, 1958) since no distinction on the basis of such studies can be drawn regarding the specific distribution of chemo-receptor and baroreceptor afferents. The use of neurophysiological techniques, how-ever, is beginning to reveal something of the specific central projections of individual baroreceptor afferents (Donoghue, Garcia, Jordan & Spyer, 1982 a).

These electrophysiological studies have been undertaken in both cat and rabbit and mainly concern the central projections of the aortic baroreceptors. In the rabbit the AN is considered to be solely barosensory, which has facilitated these studies. Briefly, the activity of the cell bodies of aortic baroreceptor afferents are recorded from the *nodose ganglion* using microelectrodes, their central projections being identified by stimulating within the *medulla oblongata* using microelectrodes and mapping the points from which an *antidromic* action potential can be evoked in the ganglion cell under investigation (Donoghue *et al.* 1982 a). Fig. 2 illustrates some aspects of the technique and Fig. 3 shows the results of an investigation into the central projection of a single aortic baroreceptor neurone with a myelinated axon, recorded in the cat nodose ganglion. By analysing both the latency of the response and the threshold for evoking the antidromic response during multiple penetrations through the dorsomedial medulla, it is possible to infer the course of the axon and its points of branching, and probably also its sites of termination (Donoghue *et al.* 1982 a, b). Our data indicate that the aortic baroreceptor afferents project to either medial or lateral, including ventrolateral, subnuclei or both, in the cat, but pre-dominantly to lateral, including ventrolateral, subnucleus in the rabbit, although in one case an exclusive and extensive projection to the medial subnucleus has been seen (Donoghue *et al.* 1982 a). Experiments are currently proceeding in the cat in which the pattern of projection of individual carotid sinus baroreceptor afferents are being studied (Donoghue, Felder, Jordan & Spyer, 1982 and in preparation). The activity of their cell bodies in the petrosal ganglion is recorded and the anti-dromic stimulation procedure described above is employed. Preliminary observations indicate that those baroreceptor afferents with both myelinated and unmyelinated axons also have widespread projections throughout much of the NTS with a pattern of branching and probable terminations that closely resembles that of AN baro-receptors, described above (Donoghue *et al.* 1982 a). In addition, data have been obtained regarding the projections of carotid body chemoreceptor afferents, with unmyelinated axons, which have a different and more restricted distribution within the NTS. There are considerable other data available in the literature con-cerning the projections of myelinated and non-myelinated AN fibres in the cat (Donoghue, Fox, Kidd & McWilam, 1981 a) and non-myelinated fibres from the heart and lungs (Donoghue *et al.* 1981 b), all of which relay to areas of the NTS shown to receive baroreceptor inputs.

These observations have extended the data obtained from previous neuroanatomical and neurophysiological studies (for review, see Spyer, 1981) and indicate a con-siderable overlap of the inputs from the AN and SN, and more specifically the
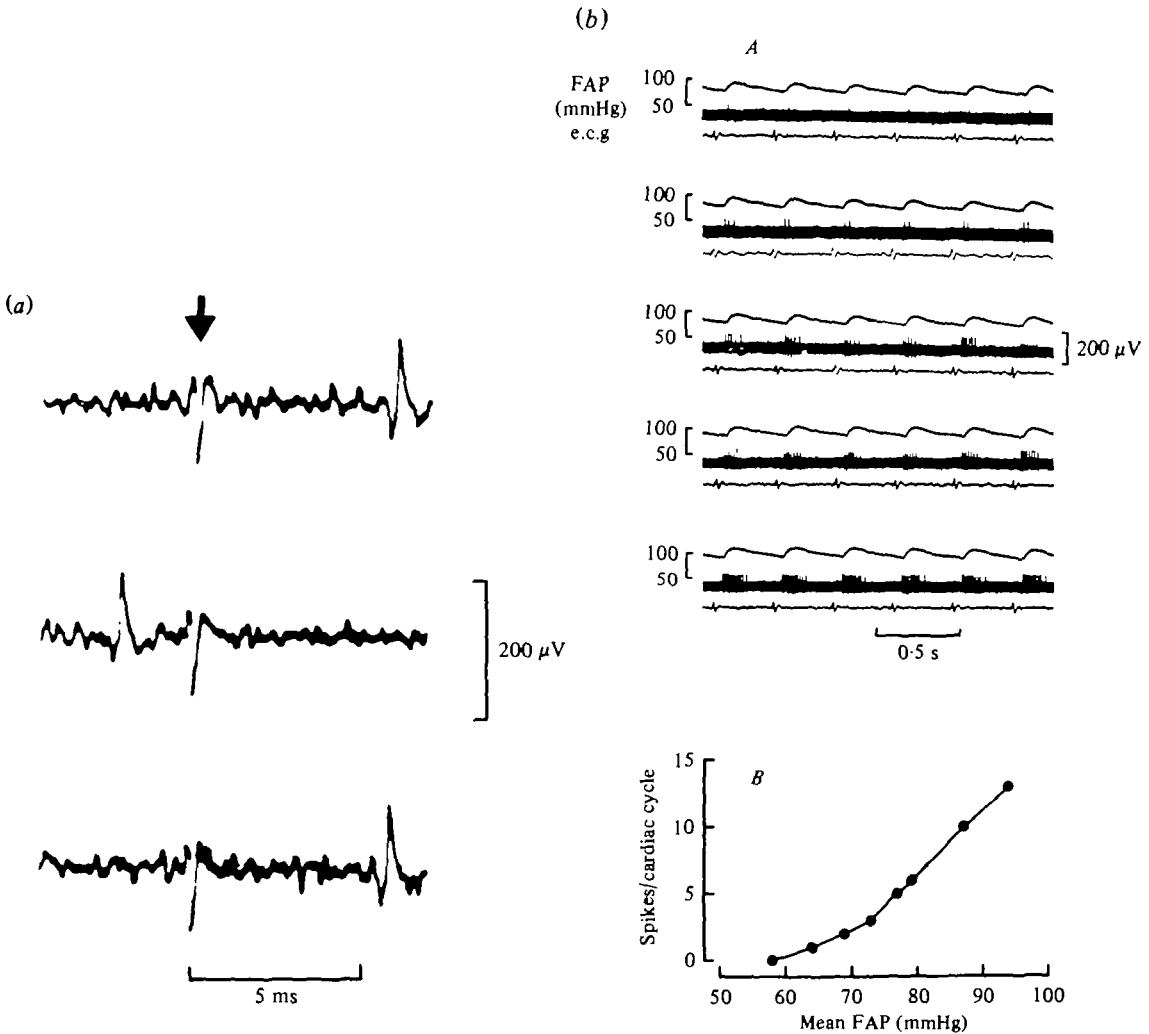
(b)

Fig. 2. (a) Cat: baroreceptor afferent. Oscilloscope traces showing three consecutive responses of the afferent shown in Fig. 5 to medullary stimulation. Stimulus artifacts are indicated by the arrow. In the top and bottom traces the stimuli each produce one antidromic action potential with a latency of 5·7 ms. In the middle trace a spontaneous action potential occurring 2·1 ms before the stimulus 'collides' with the antidromic potential, so cancelling it.

(b) Cat. (A) Original records of femoral arterial blood pressure (FAP), electrocardiogram (e.c.g.) and spontaneous activity of the aortic baroreceptor afferent, identified in (a) showing the relationship between FAP and afferent activity. (B) A graph of number of spikes/cardiac cycle (average of ten cycles) against mean FAP. (Donoghue *et al.* 1982*a*.)

baroreceptor afferents contained in these nerves. The immediate question is whether this implies a convergence of these inputs onto neurones in the various subnuclei, a convergence which might underline the interaction between baroreceptor inputs which has been readily demonstrated (see Spyer, 1981 for references). As yet the answer is uncertain. A lack of convergence of inputs from SN and AN in the NTS has been claimed although it was readily demonstrated beyond the confines of the nucleus (Biscoe & Sampson, 1970; McAllen, 1973). In a more recent study, Ciriello
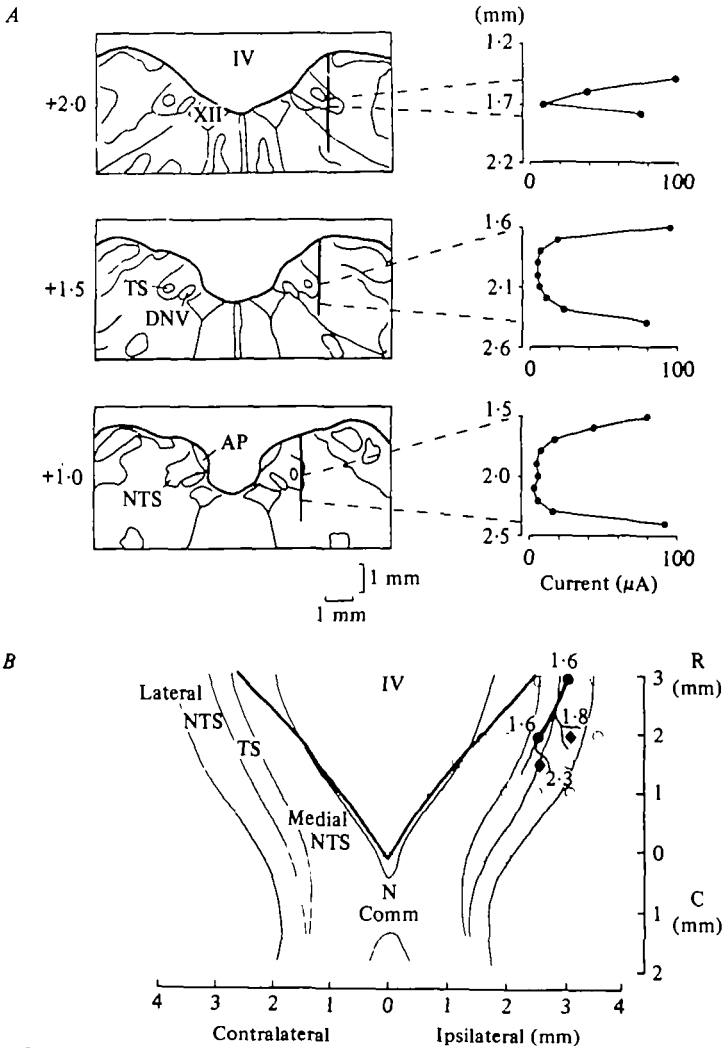
Fig. 3. Cat: baroreceptor afferent. (A) Cross-sections of the dorsomedial region of the medulla oblongata at 0·5 mm intervals from 1 mm rostral (+1) to 2 mm rostral (+2) to the obex. The thick vertical lines each represent a stimulating electrode penetration. On the right are shown depth-threshold curves corresponding to the penetrations. That at the top is of the 'point' type, the lower two of the 'field' type. (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 penetration are indicated, classed according to the type of depth-threshold contour obtained from the penetration, i.e. point (●), field (◆) or no response (○). The main axon is shown by the thick line connecting point types, and regions of branching by the thin lines. Abbreviations: Area postrema (AP), dorsal motor nucleus of vagus (DNV), nucleus commissuralis (NComm), nucleus tractus solitarius (n.t.s.), tractus solitarius (t.s.), hypoglossal nucleus (XII) and IVth ventricle (IV). (Donoghue et al. 1982a.)

& Calaresu (1981) have provided convincing evidence of convergence of these inputs onto neurones located within the medial, parvocellular, ventrolateral and intermediate subnuclei, but more specifically in areas adjacent to the nucleus.

In addition to the data from extracellular recording studies, Donoghue, Felder, Jordan & Spyer (unpublished material) have found evidence in intracellular recordi

studies that some NTS neurones receive convergent excitatory inputs from AN and SN but the majority appear to respond to one or the other input. In only a few cases was it clear that the cells responded to baroreceptor inputs specifically as shown by changes in membrane potential and spike discharge closely correlated to the e.c.g. In addition, a powerful inhibitory input from both SN and AN was seen in several NTS neurones. The localization and morphology of these different categories of neurones remain to be resolved.

This relative paucity of information concerning the specific organization of the baroreceptor reflex from these recent studies is fortunately supplemented by earlier observations. Lipski, McAllen & Spyer (1975) described neurones grouped mainly in the lateral and ventrolateral portions of the intermediate NTS of the cat's medulla, but with some in parvocellular and commissural subnuclei, that were excited by both SN stimulation and specific baroreceptor stimulation. Some neurones with this pattern of input were also shown to have axons which descended at least as far as the cervical spinal cord (Lipski & Trzebski, 1975). Using a rather different approach, Miura & Reis (1972) have described baroreceptor sensitive neurones in both medial and parvocellular portions of the NTS; the pulse rhythmic discharge of these cells was abolished by bilateral carotid occlusion. Similarly, Langhorst and his colleagues (Stroh-Werz, Langhorst & Camerer, 1977a, b) have described neurones in this general area of the NTS of both cat and dog, that have both cardiac-related activity and also respiratory modulated discharge. In no case was conclusive evidence provided that the cardiac rhythm was dependent on inputs from the aortic and carotid sinus baroreceptors.

Together this information has led to a controversy as to whether 'medial' or 'ventrolateral' portions of the NTS represent the primary integrative 'centre' in the baroreceptor reflex (see Spyer, 1981). The extensive projections of individual baroreceptor afferents described here may provide an explanation for this apparent dichotomy. There seems no doubt that both general areas receive an input from the arterial baroreceptors, and in fact a single baroreceptor afferent may innervate both areas. This underlines the importance of establishing the physiological properties of neurones in these areas and their functional connections both within and beyond the NTS.

Modifications of transmission of baroreceptor information within the NTS

Respiratory influences. The NTS contains one of the major groups of brainstem respiratory neurones (Richter, 1982) and receives a marked innervation from vagal lung stretch afferents (Donoghue *et al.* 1982b). This has led to speculations that at least part of the modifications of the efficacy of the baroreceptor reflex (and chemoreceptor reflex) that occur during the respiratory cycle might be accomplished by changes in either the excitability of NTS neurones or their afferent inputs (Koepchen, Wagner & Lux, 1961; Gabriel & Seller, 1970; Jordan & Spyer, 1979). This possibility has wider implications since if it were proven it would emphasize the integrative role of this nucleus in cardiovascular control.

One mechanism that has been considered as a possible factor in these changes is a presynaptic 'gating' of the afferent input to NTS neurones. Studies so far indicate, however, that baroreceptor and chemoreceptor afferents terminating within the NTS

are not amenable to modulation of their terminal excitability. This is based on the observations that the threshold for evoking antidromic discharge in nodose ganglion AN neurones and the membrane potential of AN afferents recorded within the NTS showed no fluctuations in phase with respiratory activity (Ballantyne *et al.* 1981).

This, however, does not eliminate a role for the NTS in modifying the performance of the baroreceptor reflex. There is plentiful evidence that the activity of many neurones in the NTS, which are not within the category of classical 'respiratory' neurones as discussed by Richter (1982), may show alterations in discharge related to respiratory activity as well as cardiac related discharge (Stroh-Werz *et al.* 1977 b). Were these cells interneurones, receiving respiratory influences and baroreceptor inputs, their output would depend on the summation of these inputs. The data available so far are hardly compelling since neurones with cardiac-related rhythmicity may either show maximal or minimal discharge in phase with inspiration (Stroh-Werz *et al.* 1977 b). The absence of an homogenous pattern of convergence underlines the need to identify the individual neuronal connections of these cell types. There is most certainly no evidence for an 'all or nothing' gating of the reflex input within the NTS, and any 'gating' would seem to act by synaptic processes remote from the primary afferent terminals.

The defence reaction. During the defence reaction evoked by electrical stimulation within a circumscribed region of the hypothalamus, the baroreceptor reflex may be totally suppressed, and this suppression is affected within the central nervous system (Coote, Hilton & Perez-Gonzalez, 1979). There is evidence for descending connections from the hypothalamus, arising probably in the vicinity of paraventricular nucleus, which contain neurophysins and terminate in several sites in the medulla, including the NTS (Saper *et al.* 1976; Swanson, 1977). As both cardiac and vascular components of the reflex appear to be blocked, and both arterial pressure, particularly pulse pressure, and heart rate rise, it has been proposed that the reflex may be blocked at an early stage in its processing, namely within the NTS (Coote *et al.* 1979).

The excitability of the baroreceptor afferent terminals is not heightened during stimulation of the hypothalamic defence area (Jordan & Spyer, 1979). There is, however, evidence that the excitatory effect of baroreceptor afferents on the NTS neurones is blocked by a conditioning stimulus to the hypothalamus (McAllen, 1976). Similar effects on the excitatory influence of SN stimulation have also been described (Adair & Manning, 1975; McAllen, 1976) although in one of these studies the stimulus to the hypothalamus had not been shown to affect the baroreceptor reflex, and the NTS neurones had not been shown to be sensitive to baroreceptor stimulation (Adair & Manning, 1975).

Together these data indicate that both peripheral and centrally arising inputs to the NTS can modify the performance of the baroreceptor (and chemoreceptor) reflex. This is certainly strong evidence for an integrative role of the NTS but as yet we have little data on the basis of the processing undertaken within the NTS that results in appropriate outputs to modify cardiovascular activity. In a general neuroanatomical sense much has recently been discovered concerning the *efferent* connections of the NTS (see Loewy & Burton, 1978; Spyer, 1981 for review). These

involve ascending pathways to the pons and diencephalon and descending connections to the spinal cord, as well as diffuse connections within the medulla. The significance of many of these connections in the physiology of cardiovascular control remains only poorly resolved. To obtain a clearer picture one must move to the output side of the CNS – the preganglionic sympathetic and vagal neurones – to obtain a critical appreciation of the role of the central nervous system in cardiac and vascular control.

II. REGULATION OF PREGANGLIONIC VAGAL ACTIVITY

The major regulation of cardiac activity, particularly chronotropic, is exerted by the vagal efferent innervation of the heart (Heymans & Neil, 1958). The mechanisms and neural pathways mediating this regulation have been the subject of intense study over the last two decades. The physiological properties of the vagal supply to the heart are now partially understood, and the baroreceptor–cardiac reflex offers some exciting opportunities for further study.

Considering the importance of this innervation, it is perhaps surprising that little was known of the site of origin of these neurones until recently. This subject has been reviewed in detail (Spyer, 1981) and a brief review is probably sufficient for the present discussion.

In birds, there is a single vagal motor nucleus in the medulla, the dorsal vagal nucleus (DVN), and there is good neurophysiological and neuroanatomical evidence that the vagal motoneurones that innervate the heart originate there (Cohen *et al.* 1970; Schwaber & Cohen, 1978*a*, *b*). In mammals, the situation is complicated by the presence of two motor nuclei – the DVN and N ambiguus (NA). Recent neurophysiological studies have shown the cardiac vagal motoneurones (CVMs) responsible for chronotropic control are located exclusively in the NA in the cat (McAllen & Spyer, 1976, 1978*a*, Fig. 4) and in both NA and DVN in the rabbit (Jordan *et al.* 1979). In the dog, CVMs have been identified in the NA but as yet there are no indications as to whether such neurones are also found in the DVN (McAllen & Spyer, unpublished observations). CVMs have small myelinated axons and there is evidence also that efferent neurones with unmyelinated axons may also innervate the heart, although their function remains uncertain (McAllen & Spyer, 1976). In a recent study, Geis & Wurster (1980) have suggested that in the cat the NA is responsible for chronotropic control, the DVN for inotropic control, presumably mediated by those vagal neurones with unmyelinated axons (McAllen & Spyer, 1976). Such a division of function seems surprising, since it is well established that any change in heart-rate produces *pari passu* a change in inotropic state. Additional claims for a wider distribution of vagal cardioinhibitory neurones in the medulla of the cat (Ciriello & Calaresu, 1980) should be viewed with caution, since a detailed analysis of the discharge pattern is necessary before neurones can be classified with certainty as cardiac in function (McAllen & Spyer, 1978*a*). Such a detailed analysis of the firing pattern in establishing a cardioinhibitory function has been undertaken in both cat and rabbit, and a general pattern of discharge has been revealed which conforms to that described for vagal fibres (McAllen & Spyer, 1978*b*; Jordan *et al.* 1979).

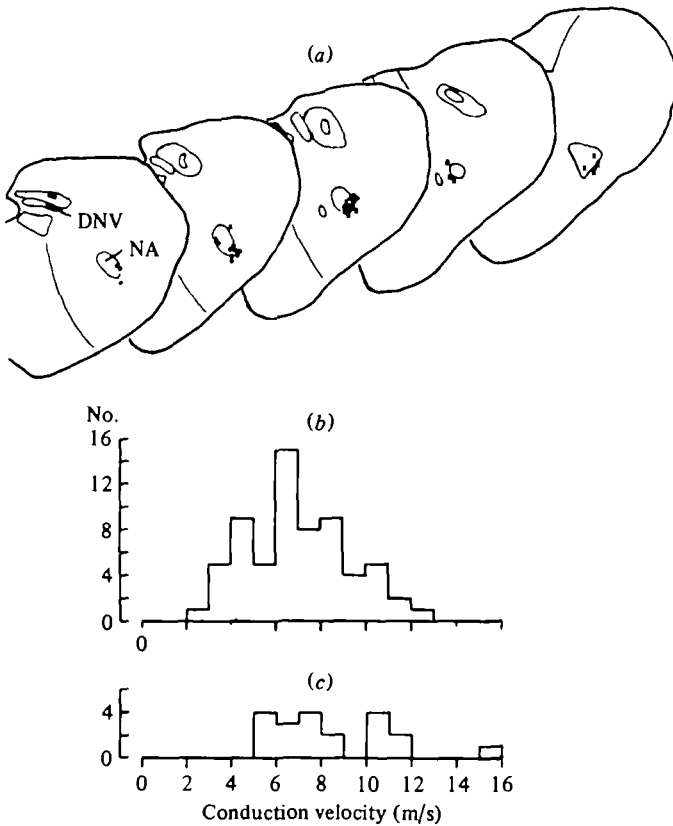*The pattern of discharge.* Vagal efferent fibres supplying the heart have been

Fig. 4. Cat. (a) The position of 21 cardiac vagal motoneurones (CVMs) (●) and nine broncho-constrictor vagal motoneurones (BVMs) (×) on five standard sections of the medulla taken at obex level, 1, 2, 3 and 4 mm rostral to the obex. DMN dorsal motor nucleus of the vagus; NA nucleus ambiguus. (b), (c) Histograms of the conduction velocities of cardiac and bronchomotor units, respectively. (McAllen & Spyer, 1978a.)

shown to fire primarily during expiration and to have a conspicuous cardiac-related rhythm (see Spyer, 1981 for references). This discharge depends largely on excitatory inputs arising from the arterial baroreceptors (Heymans & Neil, 1958). Whilst this form of discharge is readily observed in the anaesthetized dog, such activity is less apparent in the anaesthetized cat, which is notorious for having a low 'vagal tone'. Recordings from CVMs made in cat, rabbit and dog have just such a pattern of discharge (McAllen & Spyer, 1976, 1978a, b; Jordan et al. 1979) but ongoing activity is rare in the cat, although a normally subliminal fluctuation in excitability underlining such a pattern can be revealed using the microiontophoretic application of the excitant amino acids DL-homocysteic acid (DLH) or glutamate to raise the cell's excitability above firing threshold (McAllen & Spyer, 1978b).

Baroreceptor inputs to CVMs. The baroreceptor influence on CVMs is conducted by way of both SN and AN and is mediated via the NTS (see above). Stimulation of the SN has been shown to excite cardiac efferent fibres recorded in the vagal branches supplying the heart after 26–90 ms (Kunze, 1972). CVMs have been excited by SN stimulation and the effects of carotid sinus baroreceptors can be

assessed by measuring the time between the SN afferent volley and the onset of CVM activity. The latency of the reflex appears to be from 20–110 ms with some distribution into two peaks (McAllen & Spyer, 1978*b*). The input from the AN to CVMs in the rabbit acts with a latency of 6–25 ms (mean 13 ms) for neurones recorded in both DVN and NA (Jordan *et al.* 1979).

The relatively short latency influence of the arterial baroreceptors on the activity of CVMs, and the well-documented connections from the NTS to the NA in the cat (Loewy & Burton, 1978) have indicated that the baroreceptor–cardiac reflex might be mediated over a relatively direct medullary pathway. This may indeed be partially true, but the longer latency influences manifest in the study of McAllen & Spyer (1978*b*) are compatible with an additional long-circuited component in the reflex (Spyer & Jordan, 1980; Spyer, 1981). It has been speculated that this might involve the hypothalamus (Spyer, 1979, 1981) since the anterior hypothalamus is known to participate in the baroreceptor reflex (Hilton & Spyer, 1971; Spyer, 1972). Recent studies in the rabbit have shown that stimulation within regions of the diencephalon that elicit bradycardia and receive an innervation from the NTS, excites CVMs at short latency (Kaufman *et al.* 1979). Stimulation within the hypo-thalamic depressor area excites CVMs with a latency of 10–20 ms, although this input is only effective if timed to occur during expiration (Jordan *et al.*, unpublished observations). There is plentiful anatomical evidence for pathways descending from the hypothalamus to the vagal preganglionic neurones although their relevance to these electrophysiological data remain to be resolved (Loewy & McKellar, 1980).

Respiratory influences. As shown above, CVMs when active discharge usually during expiration. They are usually totally or partially refractory to excitatory inputs, such as those arising from the arterial baroreceptors or the hypothalamus during inspiration (see for example, McAllen & Spyer, 1978*b*; McCloskey & Potter, 1981). In the cat, McAllen & Spyer (1978*b*) have shown that if the excitability of CVMs is raised by the direct effects of iontophoresed amino acids, a baroreceptor and SN influence can be revealed during inspiration which is qualitatively identical to that seen during expiration (Fig. 5). McCloskey & Potter (1981) have studied the influence of both lung inflation and central inspiratory activity independently in more detail (Gandevia, McCloskey & Potter, 1978) and indicate that the latter exerts a more potent inhibitory control of CVM activity, since it blocks both phasic and tonic components of baroreceptor excitatory responses (Potter, 1981). It is worth stressing that in many of the studies cited the animals were either paralysed or had thoracotomies, so that central inspiratory activity was desynchronized from lung inflation, which was driven by a ventilator. The inability of lung inflation inputs to affect the more tonic components of baroreceptor-induced discharge is suggested to indicate a separate site of action of this respiratory input to that of central inspiratory drive (Potter, 1981).

The overall observations relating to modifications of the efficacy of the baroreceptor reflex with respiration, vagal activity and heart rate cited above coincide with other observations in an expansive literature (see for example, Daly, 1972). They account well for the experimental studies of Anrep, Pascual & Rössler (1936*a*, *b*) which outlined the factors responsible for sinus arrhythmia.

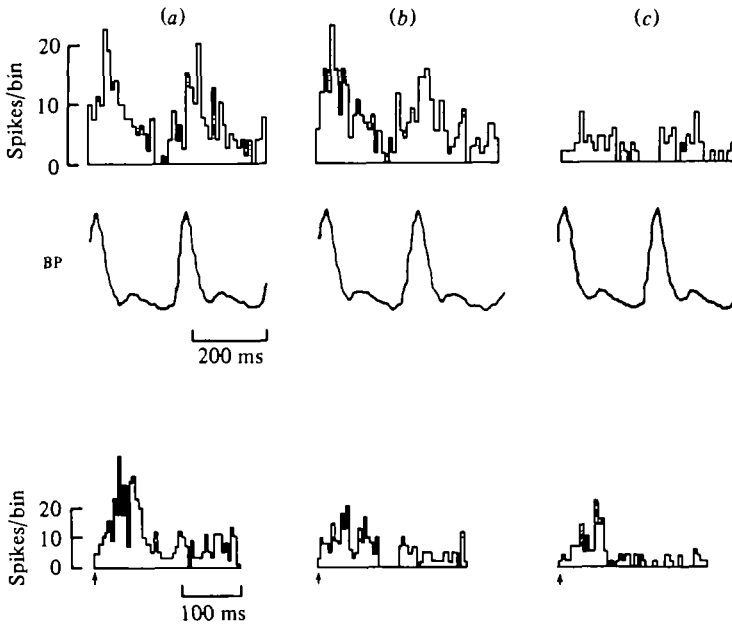The neural mechanisms underlying the changing responsiveness of CVMs to

Fig. 5. Cat. Cardiac rhythm of a cardiac vagal motoneurone (CVM) and its response to stimulation of the sinus nerve. Trace from top downwards: pulse-triggered histograms of CVM activity (120 cycles, 10 ms bins) with femoral pulse wave (BP) on same time scale, histograms of response to sinus nerve stimulation (0·1 ms pulse at 2 V, 128 cycles, 5 ms bin width). (a) Analysed throughout the respiratory cycle; (b) analysed in expiration; (c) analysed in inspiration. Unit firing in response to 60 nA DLH. (McAllen & Spyer 1978b.)

their inputs, such as those from the arterial baroreceptors and chemoreceptors, have been the matters of much speculation (Lopes & Palmer, 1976a; McAllen & Spyer, 1978b; Spyer, 1981; Potter, 1981). As yet there is relatively little direct information although Garcia, Jordan & Spyer (1978) have provided neuropharmacological data to support a role of a cholinergic inhibition of CVMs in phase with the inspiration as the basis for this phenomenon. The pattern of firing of CVMs does not resemble the recruiting pattern of discharge of central expiratory neurones, a fact that has been used as an argument against an excitatory input from medullary expiratory neurones to CVMs (Spyer, 1979, 1981). As described in Spyer (1981) acetylcholine applied iontophoretically onto CVMs firing in response to DLH produces a dose-dependent inhibition, which is antagonized by the iontophoresis of atropine (Garcia et al. 1978). Atropine alone evokes an increase in CVM discharge, causing the neurone to fire during inspiration when it is normally silent. There is only a minor increase in the ongoing expiratory discharge, which suggests that atropine is blocking a phasic inhibitory input. Fig. 6 illustrates a schematic representation of the neuronal mechanisms that may account for these observations, which suggests that neighbouring inspiratory neurones may directly innervate and inhibit CVMs. This proposal of an inhibitory cholinergic synapse has received additional support from a neuropharmacological study on the interactions between medullary respiratory neurones (Jordan & Spyer, 1981). Since it is widely accepted that expiratory neurones are actively inhibited during inspiration (Richter, Heyde & Gabriel, 1975) it seemed
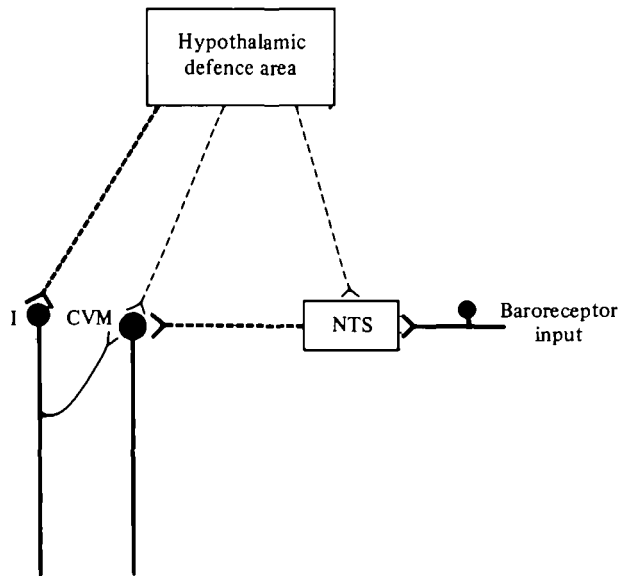
Fig. 6. Diagram illustrating the control of the baroreceptor input to cardiac vagal moto-neurone (CVM). Inspiratory neurones of the NA (I) exert an inhibitory control of CVM. This inhibitory mechanism is sensitive to atropine. The hypothalamic defence area may inhibit CVM activity and block their baroreceptor input through this mechanism, but also by an alternative mechanism. This may involve a direct inhibitory control of CVM, or via a modification of transmission through the *NTS*. See text for further details. *Dotted lines* represent pathways of unknown synaptic complexity, excitatory pathways are shown by *thick lines*, inhibitory by *thin lines*. (Modified from Spyer, 1981.)

a reasonable suggestion that a common transmitter would mediate the inspiratory silencing of CVMs and expiratory neurones (Jordan & Spyer, 1981). The ionto-phoretic application of ACh to CVMs (Garcia *et al.* 1978) and expiratory neurones (Jordan & Spyer, 1981) evokes inhibition, an effect which is antagonized by atropine but not β-dihydroerythrodiene (Jordan & Spyer, 1981). Since the iontophoretic application of atropine alone evokes firing in both classes of neurone during inspiration, it appears that this action of ACh is likely to be direct rather than via an inhibitory interneurone which is excited by ACh; inspiratory firing neurones in the NA are not excited by ACh (Jordan & Spyer, 1981).

On the basis of this evidence it appeared that the excitability of CVMs was largely determined by this inspiratory related mechanism. It has been postulated that the inhibitory effects of lung inflation could be accounted for by the involvement of the $R\beta$ group of inspiratory neurones (Lopes & Palmer, 1976), neurones that are located in the NTS and are excited by both central inspiratory drive and afferent vagal inputs driven by lung inflation (Baumgarten & Kanzow, 1958). These neurones most certainly project to the NA (Merrill, 1974) but there are differences in the efficacy of central inspiratory activity and lung inflation in modifying CVM dis-charge and the baroreceptor–cardiac reflex (Potter, 1981). This indicates that two independent processes may be involved.

Centrally evoked modifications. In addition to the respiratory related influences on CVM activity and their reflex inputs, it is known that heart rate changes mediated
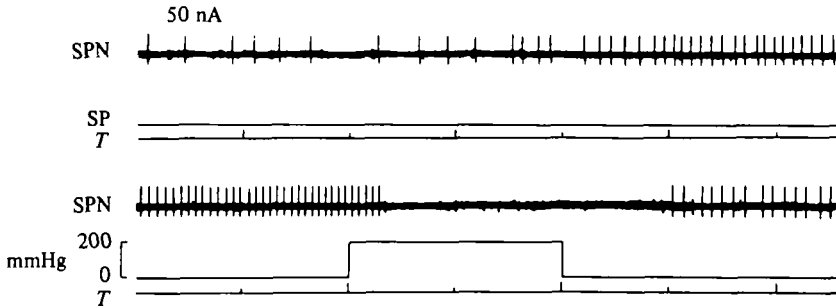
Fig. 7. The effect of an abrupt rise in sinus pressure (SP; redrawn) on the high-frequency (31 Hz) discharge of a single sympathetic preganglionic neurone (SPN) produced by the microelectrophoretic application of glutamate (50 nA) at beginning of top trace. Time trace T, 1 s. Records retouched. (Coote et al. 1981a.)

by alteration in vagal efferent activity can be elicited by stimulating several sites in the central nervous system. The synaptic processes underlying these responses are poorly illustrated, but in the case of the defence reaction evoked by stimulating within the hypothalamus certain possible mechanisms are emerging.

It has long been known that the cardiac component of the baroreceptor reflex is susceptible to central resetting (Spyer, 1981). With respect to the defence reaction both cardiac and vascular components appear susceptible to central inhibition (Coote et al. 1979). Since changes in respiratory activity accompany such centrally evoked cardiovascular responses the respiratory modifications of the baroreceptor reflex which have been summarized above might contribute significantly, if not totally, to the apparent resetting of the baroreceptor–vagal reflex.

With respect to defence reaction elicited by stimulating within the hypothalamus, there is clear evidence that this produces a suppression both of CVM discharge and of the excitatory response to AN stimulation (Jordan et al. 1981). This influence of hypothalamic stimulation could be observed at low frequencies of stimulation (i.e. 1·5 Hz) at which minimal cardiovascular changes, and no respiratory effects, were noted and the responses were not modified by the iontophoretic application of atropine on to the CVM under investigation, although this had its typical effect on respiratory fluctuations in discharge (Jordan et al. 1981). These observations lend support to the contention of Lopes & Palmer (1978) that there is a tonic hypo-thalamofugal inhibitory influence on CVMs, which is independent of respiratory activity (see Fig. 6). This pathway may be important in modifying the level of CVM activity with respect to arousal, in which the defence 'regions' of the brain-stem may exert a profound influence.

III. REGULATION OF PREGANGLIONIC SYMPATHETIC ACTIVITY

In considering the role of preganglionic sympathetic neurones in the organization of cardiovascular control, one must account for the factors responsible for their ongoing discharge, which largely determines vasomotor tone, and their regulation by central structures. The traditionally accepted view has been that sympathetic tonic activity is dependent on the activity of a medullary 'vasomotor' centre

(Alexander, 1946) or 'oscillator' (Gebber & Barman, 1977). This concept has received considerable criticism over the last decade (Hilton, 1975; Hilton & Spyer, 1980), although some more recent data have indicated that a circumscribed region on the ventral surface of the rostral medulla might contribute significantly to 'vasomotor' tone (Feldberg, 1980; Guertzenstein *et al.* 1978; Hilton, 1982), as well as mediating hypothalamic and mid-brain excitatory drives to the sympathetic preganglionic neurones (Donoghue *et al.* 1981). Since relatively little is known of the neuronal inputs to and connections of the neurones of that area (Loewy, Wallach & McKellar, 1981), little discussion of its role in the integration of cardiovascular control will enter this report.

Implicit in the hypothesis of a 'vasomotor' centre was the idea that baroreceptor regulation of sympathetic activity was mediated by an active suppression of a descending excitatory drive emanating from this level of the brain which was responsible for the tonic discharge of these neurones. There is plentiful evidence of common rhythms of discharge in brainstem, and particularly medullary, reticular neurones and sympathetic preganglionic discharge (Langhorst *et al.* 1975; Gebber & Barman, 1977). The commonest is a 2–6 Hz rhythm, related to the cardiac cycle which is considered to be an intrinsic brainstem rhythm to which the baroreceptor input becomes entrained (Gebber & Barman, 1977, 1980). This rhythm appears commonly in neurones of the *N. reticularis gigantocellularis* (Barman & Gebber, 1980), which is known to contain bulbospinal neurones. As yet the neural connections between these brainstem 'oscillators' and sympathetic preganglionic neurones have not been studied experimentally.

Regarding the pathway for excitatory control of sympathetic neurones, there is evidence of a descending pathway passing through the dorsolateral funiculus of the cervical spinal cord (Coote & Macleod, 1974*a, b*, 1975; Geis, Barratt & Wurster, 1978). Whether this is directly related in the mediation of the patterns of excitatory control described above is not certain, but lesions in this specific region of cervical spinal cord severely modify the normal excitatory responses observed on hypothalamic and cerebellar stimulation (Achari, Al-Ubaidy & Downman, 1978).

Lesions in this same region of the cervical spinal cord also modify or partially abolish the baroreceptor control of sympathetic discharge (Coote & Macleod, 1974*b*, 1975). This does not appear to be a consequence of simply removing a tonic excitatory drive but rather represents the removal of a descending inhibitory control (Coote & Macleod, 1975). This suggestion had been considered controversial since its demonstration depended on rather small changes in spinal mediated reflexes into sympathetic nerves (Coote & Macleod, 1974*b*) but recent studies have shown that the activity of single sympathetic neurones recorded with microelectrodes in the intermediolateral cell column and firing in response to iontophoretically applied glutamate is silenced by baroreceptor stimulation (Coote *et al.* 1981*a*). Further, this glutamate-evoked discharge, or ongoing firing in these cells, was inhibited by the iontophoretic application of noradrenaline; adrenaline and dopamine were also effective (Coote *et al.* 1981*b*). Previous studies had indicated that the A1 group of noradrenaline-containing neurones, located in the region of the lateral reticular nucleus, had connections with the intermediolateral cell column of the spinal cord via a pathway

through the DLF of the cervical spinal cord (Coote & Macleod, 1974a; Fleetwood-Walker & Coote, 1981). Other reports question whether this pathway is truly nor adrenergic (Blessing, West & Chalmers, 1981; West, Blessing & Chalmers, 1981) but there appear compelling reasons to consider that this is likely and that this pathway is a major means by which the baroreceptors exert their control of sympathetic discharge.

In this same study Coote et al. (1981b) showed that serotonin, applied ionto-phoretically to preganglionic sympathetic neurones, evoked an excitatory response. Serotinergic neurones are grouped in several regions of the brainstem including the raphe complex but the electrical stimulation of this area evokes sympathoinhibition (Coote & Macleod, 1975). This inhibitory action is not concerned with the baro-receptor control of sympathetic activity (Coote & Macleod, 1975). In addition, the B3 group of serotinergic neurones, which may correspond to the ventral medullary 'vasomotor' neurones, have been shown to have a spinal projection (Loewy, Wallach & McKellar, 1981). This may well provide the first detailed description of an excita-tory bulbospinal pathway to sympathetic neurones.

It would appear from the previous discussion that a specific inhibitory pathway, and two excitatory pathways (amongst several other possible pathways, both inhibitory and excitatory) have been identified which influence the pattern of discharge of sympathetic neurones (reviewed by Spyer, 1981). To this must be added the seg-mental and suprasegmental connections mediating somatic and visceral afferent reflex control of sympathetic discharge (Wurster, 1977; Coote, 1978). These data imply an important integrative role of the preganglionic neurone in the moment-by-moment regulation of cardiovascular system (Spyer, 1981). It may well be that most interactions between reflex inputs and centrally elaborated drives can be explained on the basis of summation at this level. It is known that intrinsic properties of these preganglionic neurones contribute to a narrow firing range so that saturation at one end and silence at the other can readily be evoked by additive influences (Polosa, 1967, 1968; Polosa, Mannard & Laskey, 1979).

This suggestion may well argue against 'gating' being involved in either the defence area suppression of the baroreceptor reflex, or the modifications of the reflex during the respiratory cycle. The available evidence makes it unlikely that either influence exerts an *all or nothing* 'gating' of the baroreceptor input at the level of the NTS (see above), although modifications may well occur. There is as yet no neurophysiological evidence relating to the interactions of baroreceptor inputs and the 'defence' pathway at other sites within the brainstem, except in the case of cardiac vagal motoneurones (see above), but this must be considered likely in view of studies on the patterns of discharge of neurones in the 'common brain-stem' system which have multi-sensorial inputs (Langhorst et al. 1980). Depending on the balance of the two drives, one excitatory (defence) and one inhibitory (baro-receptor), it is possible to imagine changes in the efficacy of many of the descending pathways, culminating in a final output, sympathetic discharge, that is dominated by one or other. Essentially this is an example of summation and is very much the pattern of interaction that is responsible for the respiratory modifications of baro-receptor control of the heart mediated by sympathetic efferents. It is firmly established

that just as the baroreceptor–vagal reflex is modified by inspiration, so the baro-receptor–sympathetic component of the reflex is similarly affected (Seller *et al.* 1968; Seller & Richter, 1971; Davis, McCloskey & Potter, 1977). The duration of the silencing of sympathetic activity evoked by the baroreceptors was shown to be minimal in the middle of inspiration, i.e. peak of the phrenic nerve discharge, and maximal shortly after the cessation of inspiration (Seller & Richter, 1971). As it is believed that inspiratory neuronal discharge provides an excitatory drive to sympathetic neurones, at the end of inspiration the baroreceptor input would be timed to arrive at a 'disfacilitated' neurone, and hence a neurone readily affected by an inhibitory input. The respiratory influence does not, however, appear to be as powerful in effect as the inspiratory 'gating' of vagal efferent discharge described above.

REFERENCES

ACHARI, N. K., AL-UBAIDY, S. S. & DOWNMAN, C. B. B. (1978). Spinal sympathoexcitatory pathways activated by stimulating fastigial nuclei, hypothalamus and lower brain stem in cats. *Expl Neurol.* **62**, 230–240.

ADAIR, J. R. & MANNING, J. W. (1975). Hypothalamic modulation of baroreceptor afferent unit activity. *Am. J. Physiol.* **229**, 1357–1364.

ALEXANDER, R. S. (1946). Tonic and reflex functions of medullary sympathetic centers. *J. Neurophysiol.* **9**, 205–217.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936a). Respiratory variations of heart rate. I. The reflex mechanism of the respiratory arrhythmia. *Proc. R. Soc. Lond.* B **119**, 191–217.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936b). Respiratory variations of the heart-rate. II. The central mechanism of respiratory arrhythmia and the inter-relationships between central and reflex mechanisms. *Proc. R. Soc. Lond.* B **119**, 218–230.

BALLANTYNE, D., DONOGHUE, S., JORDAN, D., MEESMANN, M., RICHTER, D. W. & SPYER, K. M. (1981). Respiratory influences on vagal afferent endings in the medulla: a study on baroreceptor and lung stretch neurones. *J. Physiol., Lond.* **312**, 28P.

BARMAN, S. M. & GEBBER, G. L. (1980). Sympathetic nerve rhythm of brainstem origin. *Am. J. Physiol.* **239**, 42–47.

BAUMGARTEN, R. VON & KANZOW, E. (1958). The interaction of two types of inspiratory neurones in the region of the tractus solitarius of the cat. *Archs ital. Biol.* **96**, 361–373.

BERGER, A. J. (1979). Distribution of carotid sinus nerve afferent fibers to solitary tract nuclei of the cat using transganglionic transport of horseradish peroxidase. *Neurosci. Lett.* **14**, 153–158.

BERGER, A. J. (1980). The distribution of the cat's carotid sinus nerve afferent and efferent cell bodies using the horseradish peroxidase technique. *Brain Res.* **190**, 309–320.

BISCOE, T. J. & SAMPSON, S. R. (1970). Responses of cells in the brainstem of the cat to stimulation of the sinus, glossopharyngeal, aortic and superior laryngeal nerves. *J. Physiol., Lond.* **209**, 359–373.

BLESSING, W. W., WEST, M. J. & CHALMERS, J. (1981). Hypertension, bradycardia, and pulmonary edema in the conscious rabbit after brainstem lesions coinciding with the A1 group of catecholamine neurones. *Circulation Res.* **49**(4), 949–958.

CIRIELLO, J. & CALARESU, F. R. (1980). Distribution of vagal cardioinhibitory neurons in the medulla of the cat. *Am. J. Physiol.* **238**, 57–64.

CIRIELLO, J. & CALARESU, F. R. (1981). Projections from buffer nerves to the nucleus of the solitary tract: an anatomical and electrophysiological study in the cat. *J. auton. Nerv. Syst.* **3**, 299–310.

CIRIELLO, J., HRYCYSHYN, A. W. & CALARESU, F. R. (1981). Horseradish peroxidase study of brain stem projections of carotid sinus and aortic depressor nerves in the cat. *J. auton. Nerv. Syst.* **4**, 43–61.

COHEN, D. H., SCHNALL, A. M., MACDONALD, R. L. & PITTS, L. H. (1970). Medullary cells of origin of vagal cardioinhibitory fibres in the pigeon. I. Anatomical structure of peripheral vagus nerves and the dorsal motor nucleus. *J. comp. Neurol.* **140**, 299–320.

COOTE, J. H. (1978). Afferent input as factors in aberrant autonomic, sensory and motor function. In *The Neurobiologic Mechanisms in Manipulative Therapy* (ed. I. M. Korr), pp. 91–127. New York: Plenum.

COOTE, J. H., HILTON, S. M. & PEREZ-GONZALEZ, J. F. (1979). Inhibition of the baroreceptor reflex on stimulation in the brainstem defence centre. *J. Physiol.* **288**, 549–560.

COOTE, J. H. & MACLEOD, V. H. (1974a). The influence of bulbospinal monoaminergic pathways on sympathetic nerve activity. *J. Physiol., Lond.* **241**, 453–457.

COOTE, J. H. & MACLEOD, V. H. (1974b). Evidence for the involvement in the baroreceptor reflex of a descending inhibitory pathway. *J. Physiol., Lond.* **241**, 477–496.

COOTE, J. H. & MACLEOD, V. H. (1975). The spinal route of sympatho-inhibitory pathways descending from the medulla oblongata. *Pflügers Arch.* **359**, 335–347.

COOTE, J. H., MACLEOD, V. H., FLEETWOOD-WALKER, S. M. & GILBEY, M. P. (1981a). Baroreceptor inhibition of sympathetic activity at a spinal site. *Brain Res.* **220**, 81–93.

COOTE, J. H., MACLEOD, V. H., FLEETWOOD-WALKER, S. & GILBEY, M. P. (1981b). The response of individual sympathetic preganglionic neurones to microelectrophoretically applied endogenous monoamines. *Brain Res.* **215**, 135–145.

DALY, M. DE B. (1972). Interaction of cardiovascular reflexes. In *Scientific Basis of Medicine Annual Review*, pp. 307–332.

DAVIES, R. O. & KALIA, M. (1981). Carotid sinus nerve projections to the brain stem in the cat. *Brain Res. Bulletin* **6**, 531–541.

DAVIS, A. L., McCLOSKEY, D. I. & POTTER, E. K. (1977). Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate through the sympathetic nervous system. *J. Physiol., Lond.* **272**, 691–703.

DONOGHUE, S., FELDER, R. B., JORDAN, D. & SPYER, K. M. (1982). Brain stem projections of carotid baroreceptors and chemoreceptors in the cat. *J. Physiol., Lond.* (in the Press).

DONOGHUE, S., FOX, R. E., KIDD, C. & KOLEY, B. N. (1981a). The distribution in the cat brain stem of neurones activated by vagal non-myelinated fibres from the heart and lungs. *Q. Jl exp. Physiol.* **66**, 391–404.

DONOGHUE, S., FOX, R. E., KIDD, C. & McWILLIAM, P. N. (1981b). The terminations and secondary projections of myelinated and non-myelinated fibres of the aortic nerve in the cat. *Q. Jl exp. Physiol.* **66**, 405–422.

DONOGHUE, S., GARCIA, M., JORDAN, D. & SPYER, K. M. (1982a). Identification and brain-stem projections of aortic baroreceptor afferent neurones in nodose ganglia of cats and rabbits. *J. Physiol., Lond.* **322**, 337–352.

DONOGHUE, S., GARCIA, M., JORDAN, D. & SPYER, K. M. (1982b). The brain-stem projections of pulmonary stretch afferent neurones in cats and rabbits. *J. Physiol., Lond.* **322**, 353–363.

DONOGHUE, S., HILTON, S. M., SMITH, P. R. & TIMMS, R. J. (1981). Inputs from the brain stem defence areas to ventral medulla neurones in the cat. *J. Physiol., Lond.* **319**, 116P.

FELDBERG, W. (1980). Cardiovascular effects of drugs acting on the ventral surface of the brain stem. In *Central Interactions Between Respiratory and Cardiovascular Control Systems* (ed. H. P. Koepchen, S. M. Hilton and A. Trzebski), pp. 47–55. Berlin: Springer-Verlag.

FLEETWOOD-WALKER, S. M. & COOTE, J. H. (1981). The contribution of brain stem catecholamine cell groups to the innervation of the sympathetic lateral cell column. *Brain Res.* **205**, 141–155.

GABRIEL, M. & SELLER, H. (1970). Interaction of baroreceptor afferents from carotid sinus and aorta at the nucleus tractus solitarii. *Pflügers Arch.* **318**, 7–20.

GANDEVIA, S. C., McCLOSKEY, D. I. & POTTER, E. K. (1978). Inhibition of baroreceptor and chemoreceptor reflexes on heart rate by afferents from the lungs. *J. Physiol., Lond.* **276**, 369–381.

GARCIA, M., JORDAN, D. & SPYER, K. M. (1978). Studies on the properties of cardiac vagal neurones. *Neurosci. Lett.* (Suppl.) **1**, S16.

GEBBER, G. L. & BARMAN, S. M. (1977). Brainstem vasomotor circuits involved in genesis and entrainment of sympathetic nervous rhythms. *Prog. Brain Res.* **47**, 61–76.

GEBBER, G. L. & BARMAN, S. M. (1980). Basis for 2–6 cycle/s rhythm in sympathetic nerve discharge. *Am. J. Physiol.* **239**, R48–56.

GEIS, G. S., BARRATT, G. & WURSTER, R. D. (1978). Role of descending pressor pathway in conscious and pentobarbital-anaesthetized dog. *Am. J. Physiol.* **234**, H152–156.

GEIS, G. S. & WURSTER, R. D. (1980). Cardiac responses during stimulation of the dorsal motor nucleus and nucleus ambiguus in the cat. *Circulation Res.* **46**, 606–611.

GUERTZENSTEIN, P. G., HILTON, S. M., MARSHALL, J. M. & TIMMS, R. J. (1978). Experiments on the origin of the vasomotor tone. *J. Physiol., Lond.* **275**, 78–79P.

HEYMANS, C. & NEIL, E. (1958). *Reflexogenic Areas of the Cardiovascular System.* London: Churchill.

HILTON, S. M. (1975). Ways of viewing the central nervous control of circulation – old and new. *Brain Res.* **87**, 213–219.

HILTON, S. M. (1982). (This meeting.)

HILTON, S. M. & SPYER, K. M. (1971). Participation of the anterior hypothalamus in the baroreceptor reflex. *J. Physiol., Lond.* **218**, 271–293.

HILTON, S. M. & SPYER, K. M. (1980). Central nervous regulation of vascular resistance. *A. Rev. Physiol.* **42**, 399–411.

JORDAN, D., KHALID, M. E. M., SCHNEIDERMAN, N. & SPYER, K. M. (1979). Preganglionic vagal cardiomotor neurones in the rabbit; location and properties. *J. Physiol., Lond.* **296**, 20–21.

JORDAN, D. & SPYER, K. M. (1979). Studies on the excitability of sinus nerve afferent terminals. *J. Physiol., Lond.* **297**, 123–134.

JORDAN, D. & SPYER, K. M. (1981). Effects of acetylcholine on respiratory neurones in the nucleus ambiguus-retroambigualis complex of the cat. *J. Physiol., Lond.* **320**, 103–111.

KAUFMAN, M. P., HAMILTON, R. B., WALLACH, J. H., PETRIK, G. K. & SCHNEIDERMAN, N. (1979). Lateral subthalamic areas as a mediator of bradycardia responses in rabbits. *Am. J. Physiol.* **236**, H471–479.

KOEPCHEN, H. P., HILTON, S. M. & TRZEBSKI, A. (Eds) (1980). *Central Interactions between Respiratory and Cardiovascular Control Systems.* Berlin: Springer-Verlag.

KOEPCHEN, H. P., WAGNER, P. H. & LUX, H. D. (1961). Über die Zusammenhänge zwischen zentraler Erregbarkeit reflektorischen Atemrhythmus bei der nervösen Steuerung der Herzfrequenz. *Pflügers Arch.* **273**, 443–465.

KUNZE, D. L., (1972). Reflex discharge patterns of cardiac vagal efferent fibres. *J. Physiol., Lond.* **222**, 1–15.

LANGHORST, P., SCHULZ, B., LAMBERTZ, M., SCHULZ, G., CAMERER, H. & STROH-WERZ, M. (1980). Dynamic characteristics of the unspecific brain stem system. In *Central Interactions between Respiratory and Cardiovascular Control Systems* (ed. H. P. Koepchen, S. M. Hilton and A. Trzebski), pp. 30–41. Berlin: Springer-Verlag.

LANGHORST, P., STROH-WERZ, M., DITTMAR, K. & CAMERER, H. (1975). Facultative coupling of reticular neuronal activity with peripheral cardiovascular and central cortical rhythms. *Brain Res.* **87**, 407–418.

LIPSKI, J., MCALLEN, R. M. & SPYER, K. M. (1975). The sinus nerve and baroreceptor input to the medulla of the cat. *J. Physiol., Lond.* **251**, 61–78.

LIPSKI, J. & TRZEBSKI, A. (1975). Bulbospinal neurones activated by baroreceptor afferents and their possible role in inhibition of preganglionic sympathetic neurons. *Pflügers Arch.* **356**, 181–192.

LOEWY, A. D. & BURTON, H. (1978). Nuclei of the solitary tract. Efferent projections to the lower brainstem and spinal cord of the cat. *J. comp. Neurol.* **181**, 421–450.

LOEWY, A. D. & MCKELLAR, S. (1980). The neuroanatomical basis of central cardiovascular control. *Fedn Proc.* **39**, 2495–2503.

LOEWY, A. D., WALLACH, J. H. & MCKELLAR, S. (1981). Efferent connections of the ventral medulla oblongata in the rat. *Brain Res.* (Reviews) **3**, 63–80.

LOPES, O. U. & PALMER, J. F. (1976). Proposed respiratory 'gating' mechanisms for cardiac slowing. *Nature, Lond.* **264**, 454–456.

LOPES, O. U. & PALMER, J. F. (1978). Mechanism of hypothalamic control of cardiac component of sinus nerve reflex. *Q. Jl exp. Physiol.* **63**, 231–254.

MCALLEN, R. M. (1973). Projections of the carotid sinus baroreceptors to the medulla of the cat. Ph.D. thesis, University of Birmingham.

MCALLEN, R. M. (1976). The inhibition of the baroreceptor input to the medulla by stimulation of the hypothalamic defence area. *J. Physiol., Lond.* **257**, 45–46P.

MCALLEN, R. M. & SPYER, K. M. (1976). The location of cardiac vagal preganglionic motoneurones in the medulla of the cat. *J. Physiol., Lond.* **258**, 187–204.

MCALLEN, R. M. & SPYER, K. M. (1978a). Two types of vagal preganglionic motoneurones projecting to the heart and lungs. *J. Physiol., Lond.* **282**, 353–364.

MCALLEN, R. M. & SPYER, K. M. (1978b). The baroreceptor input to cardiac vagal motoneurones. *J. Physiol., Lond.* **282**, 365–374.

MCCLOSKEY, D. I. & POTTER, E. K. (1981). Excitation and inhibition of cardiac vagal motoneurones by electrical stimulation of the carotid sinus nerve. *J. Physiol., Lond.* **316**, 163–175.

MERRILL, E. G. (1974). Finding a respiratory function for the medullary respiratory neurons. In *Essays on the Nervous System* (ed. R. Bellairs and E. G. Gray), pp. 451–486. Oxford: Clarendon Press.

MIURA, M. & REIS, D. J. (1972). The role of the solitary and paramedian reticular nuclei in mediating cardiovascular reflex responses from carotid baro- and chemoreceptors. *J. Physiol., Lond.* **225**, 525–548.

PANNETON, W. M. & LOEWY, A. D. (1980). Projections of the carotid sinus nerve to the nucleus of the solitary tract in the cat. *Brain Res.* **191**, 239–244.

POLOSA, C. (1967). The silent period of sympathetic preganglionic neurons. *Can. J. Physiol. Pharmacol.* **45**, 1033–1045.

POLOSA, C. (1968). Spontaneous activity of sympathetic preganglionic neurons. *Can. J. Physiol. Biochem.* **46**, 587–896.

POLOSA, C., MANNARD, A. & LASKEY, W. (1979). Tonic activity of the autonomic nervous system: functions, properties, origins. In *Integrative Functions of the Autonomic System* (ed. C. McC. Brooks, K. Koizumi and A. Sato), pp. 342–354. Japan: University of Tokyo Press.

POTTER, E. K. (1981). Inspiratory inhibition of vagal responses to baroreceptor and chemoreceptor stimuli in the dog. *J. Physiol., Lond.* **316**, 177–190.

RICHTER, D. W. (1982). Generation and maintenance of the respiratory rhythm. (This meeting.)

RICHTER, D. W., HEYDE, F. & GABRIEL, M. (1975). Intracellular recordings from different types of medullary respiratory neurons of the cat. *J. Neurophysiol.* **38**, 1162–1171.

SAPER, C., LOEWY, A. D., SWANSON, L. W. & COWAN, W. N. (1976). Direct hypothalamo-autonomic connections. *Brain Res.* **117**, 305–312.

SCHWABER, J. S. & COHEN, D. H. (1978a). Electrophysiological and electron microscopic analysis of the vagus nerve of the pigeon, with particular reference to the cardiac innervation. *Brain Res.* **147**, 65–78.

SCHWABER, J. S. & COHEN, D. H. (1978b). Field potential and single unit analyses of the avian dorsal motor nucleus of the vagus and criteria for identifying vagal cardiac cells of origin. *Brain Res.* **147**, 79–90.

SELLER, H. & ILLERT, M. (1969). The localisation of the first synapse in the carotid sinus baroreceptor reflex pathway and its alteration of the afferent input. *Pflügers Arch.* **306**, 1–19.

SELLER, H., LANGHORST, P., RICHTER, D. & KOEPCHEN, H. P. (1968). Über die Abhangigkeit der pressorezeptorischen Hummung des Sympathicus von der Atemphase und ihre Auswirkung in der Vasomotorik. *Pflügers Arch.* **302**, 300–314.

SELLER, H. & RICHTER, D. W. (1971). Some quantitative aspects of the central transmission of the baroreceptor activity. In *Research in Physiology* (ed. F. F. Kao, K. Koizumi and M. Vasalle), pp. 541–545. Bologna: Gaggi.

SPYER, K. M. (1972). Baroreceptor sensitive neurones in the anterior hypothalamus of the cat. *J. Physiol., Lond.* **224**, 245–257.

SPYER, K. M. (1979). The baroreceptor control of vagal preganglionic activity. In *Integrative Functions of the Autonomic Nervous System* (ed. C. McC. Brooks, K. Koizumi and A. Sato), pp. 283–292. Japan: University of Tokyo Press.

SPYER, K. M. (1981). Neural organisation and control of the baroreceptor reflex. *Rev. Physiol. Biochem. Pharmacol.* **88**, 23–124.

SPYER, K. M. & JORDAN, D. (1980). The baroreceptor input to vagal pre-ganglionic neurons: the neural pathway and physiological control. In *Arterial Baroreceptors and Hypertension* (ed. P. Sleight), pp. 238–243. Oxford: University Press.

STROH-WERZ, M., LANGHORST, P. & CAMERER, H. (1977a). Neuronal activity with cardiac rhythm in the nucleus of the solitary tract in cats and dogs. I. Different discharge patterns related to the cardiac cycle. *Brain Res.* **133**, 65–80.

STROH-WERZ, M., LANGHORST, P. & CAMERER, H. (1977b). Neuronal activity with cardiac rhythm in the nucleus of the solitary tract in cats and dogs. II. Activity modulation in relationship to the respiratory cycle. *Brain Res.* **133**, 81–93.

SWANSON, L. W. (1977). Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. *Brain Res.* **128**, 346–353.

WALLACH, J. H. & LOEWY, A. D. (1980). Projections of the aortic nerve to the nucleus tractus solitarius in the rabbit. *Brain Res.* **188**, 247–251.

WEST, M. J., BLESSING, W. W. & CHALMERS, J. (1981). Arterial baroreceptor reflex function in the conscious rabbit after brainstem lesions coinciding with the A1 group of catecholamine neurons. *Circulation Res.* **49**, 959–970.

WURSTER, R. D. (1977). Spinal sympathetic control of the heart. In *Neural Regulation of the Heart* (ed. W. C. Randall), pp. 211–246. New York: Oxford University Press.