Handbook of Sensory Physiology

Volume III/1

Enteroceptors

Edited by E. Neil

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By

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Preface

This series of concise essays on Enteroceptors is designed to interest the graduate student and to stimulate research.

Even before the advent of electrophysiological studies, classical physiological techniques had shown the essence of the role of many of the enteroceptors. Thus the monitoring influence of the cardiovascular mechanoreceptors on the heart and on the systemic vascular resistance, the role of the arterial chemoreceptors in hypoxia and the influence of the so-called Hering Breuer stretch receptors on breathing had all been documented. The pioneering work of Adrian, Bronk, Zotterman and others using electroneurographic methods gave a remarkable impetus to the study of the enteroceptors themselves. Nowhere is this better exemplified than in the case of the afferent end organs of the heart, the respiratory tract and the abdominal and pelvic viscera. The remarkable development of our knowledge of the multiplicity of types of nerve endings from the thoracic and abdominal viscera acquired from electrophysiological studies has refocussed our attention on the histological details of the sites of such receptors. Once more research on the structural side has been accelerated by the question raised by evidence obtained from functional studies. This is well illustrated in the case of the carotid body, where the long cherished belief that the innervated epithelioid cells constitute the chemoreceptor complex is now under attack.

The detailed consideration of the functional characteristics of each enteroceptor considered has not occupied our whole attention. In so far as possible the influence of each of these afferent end organs on the organism as a whole has been considered.

Electrophysiological studies of hypothalamic neurones responsive to temperature have contributed much to our further appreciation of the complexity of thermoregulation. Techniques of electrical stimulation and/or ablation have indicated that the hypothalamic complex is concerned with relaying the sensations and behavioural activity associated with hunger and thirst. Again, electrophysiological studies have revealed the presence of anterior hypothalamic neurones responsive to changes in blood glucose levels and blood osmolality respectively, but much more evidence is required before these "central receptors" of hunger and thirst can be ascribed a firm role.

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Cardiovascular Receptors

By

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With 19 Figures

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I. Peripheral Mechanisms

Like all the other visceral receptors, the cardiovascular receptors have been studied by recording impulses in their sensory fibres most of which travel either in the glossopharyngeal or vagus nerves. So far no attempts have been made to study the precise mechanisms of impulse initiation at the ending (except in the case of the mesenteric Pacinian corpuscle described in this section), since it is practically impossible to isolate a single cardiovascular receptor and study the generator potentials produced by it. It will be necessary to await the development of techniques that will enable recording of such potentials (e.g. with microelectrodes) before one can attempt to study such processes in these endings. However, for practical purposes it is not imperative to do this because the information already available in the case of other mechanoreceptors can be applied to the cardiovascular receptors as well. For example as in the case of the muscle spindle (Katz, 1950) and the Pacinian corpuscle (Alvarez-Buylla and Ramirez de Arellano, 1953; Gray and Sato, 1953; Loewenstein and Rathkamp, 1958;

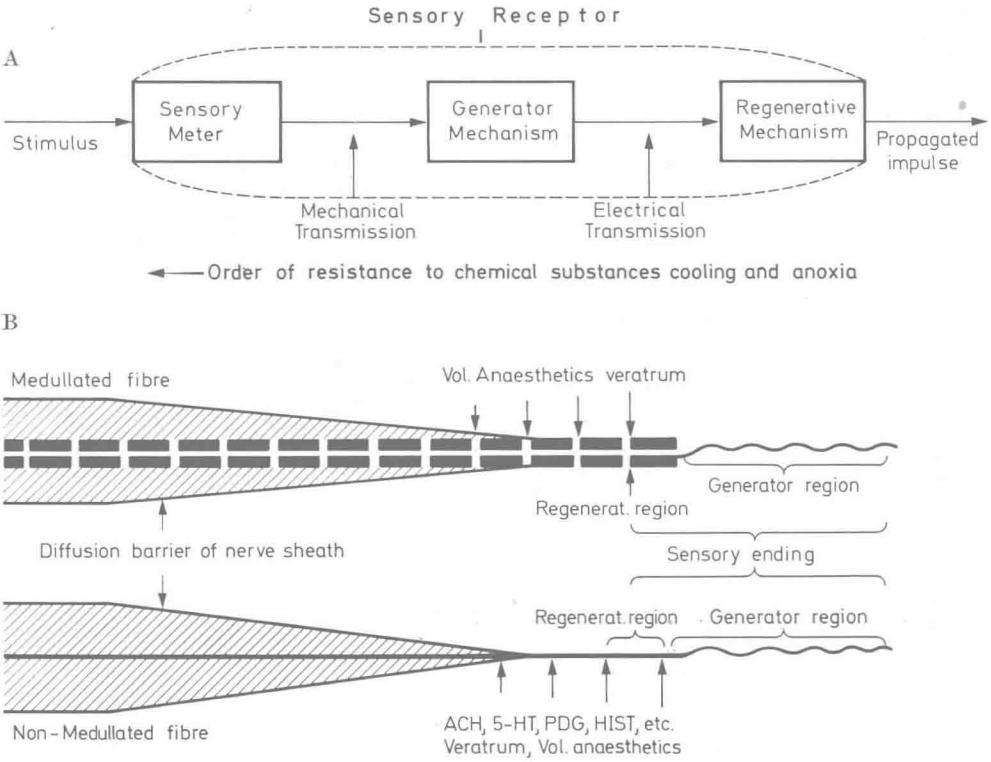

Fig. 1 A and B. Mechanisms involved in the excitation of sensory receptors and their relative resistance to chemical substances, cooling and anoxia (PAINTAL, 1971). B Schematic diagram of sensory endings of medullated and non-medullated nerve fibres showing the two parts of an ending and the probable site of action of drugs at the regenerative region, where there is no diffusion barrier. A greater variety of drugs effect the endings of non-medullated fibres because the fibres themselves are more susceptible to these drugs (PAINTAL, 1964)

for other references see PAINTAL, 1964, 1971) it may be safely assumed that impulses in cardiovascular receptors must be generated when the generator potential reaches a critical threshold for firing an impulse, that the frequency of discharge will depend on the amplitude of the generator potential, that the generator potential will be of a rhythmic nature and that as in the case of the muscle spindle it will have a dynamic off effect (KATZ, 1950) at the end of the pulsatile stimulus.

Most of the cardiovascular receptors are stimulated by certain chemical substances (see PAINTAL, 1964) or are depressed by local anaesthetics (ZIPF, 1966). It has been postulated that all these excitatory drugs and local anaesthetics produce their effects by acting on the regenerative region of the sensory apparatus as shown in Fig. 1 B (see PAINTAL, 1964). This hypothesis has received substantial support from recent experiments on muscle spindles and the crayfish stretch receptors (see PAINTAL, 1971). And so for the present it can be safely assumed that in the case of cardiovascular receptors also, the various chemical substances produce their effects by an action on the regenerative region.

It has also been brought out that the regenerative region is much more sensitive to cooling and anoxia and that there is an increasing order of resistance to chemical substances, cooling and anoxia as one proceeds backwards from the regenerative region to the stimulus (Fig. 1 A). The most resistant structures appear to be the sensory meters which in the case of cardiovascular receptors must be the fibro-elastic tissue in which the endings lie (PAINTAL, 1971). It needs to be stressed that the actual meters which transmit, by causing mechanical deformation of the generator region, the intensity of the stimulus, are the non-nervous elements i.e. the fibro-elastic tissue as far as the cardiovascular receptors are concerned. Clearly, if the stress/strain properties of this tissue changes, so will the degree of deformation of the generator region. Under experimental conditions any agent that is strong enough to put out of action the regenerative and generator regions apparently leaves the sensory meter practically unaffected (PAINTAL, 1971). However in certain diseases, e.g. TAKAYASHU'S disease (see HEYMANS and NEIL, 1958, p. 84) and possibly mitral stenosis in the case of left atrial receptors it is conceivable that the sensory meter may be affected before any changes occur at the regenerative region. For such studies i.e. alterations in the properties of the sensory meters the cardiovascular receptors may prove more useful than the Pacinian corpuscle or muscle spindle—receptors that have been the source of valuable information about generator processes.

As in the case of other mechanoreceptors (PAINTAL, 1964) there is no firm evidence that a chemical transmitter is involved in the process of impulse initiation at any stage as shown in Fig. 1 A (PAINTAL, 1971).

II. Nerve Fibres

Most of the known cardiovascular receptors are connected to medullated nerve fibres as shown in Table 1. Such receptors are therefore unaffected by chemical

Table 1. *Conduction velocities of cardiovascular afferent fibres (*PAINTAL, *1953c, 1963a and unpublished observations)*

Type of receptor	Nature of fibre (i.e. medullated or non-medullated)	Conduction velocity		
		Range (m/sec)	Mean (m/sec)	S.D. (m/sec)
Carotid baroreceptors	med.	[a]	[a]	[a]
	non-med.	0.5–2.0	—	—[b]
Aortic baroreceptors	med.	12–53	33	11
Right atrial type A	med.	13–27	20	4
Left atrial type A	med.	12–19	16	2
Right atrial type B	med.	8–29	17	6
Left atrial type B	med.	11–26	18	3
Ventricular pressure receptors	med.	8–19	13	—
Epicardial receptors	non-med.	1.2–1.9	—	—[c]
		0.4–5.0	1.5	2.3 (SE)[d]
Pericardial receptors	med.	2.5–7.0	5.3	—[e]

[a] Not known. [b] FIDONE and SATO (1969). [c] COLERIDGE *et al.* (1964b).
[d] SLEIGHT and WIDDICOMBE (1965a).
[e] SLEIGHT and WIDDICOMBE (1965b) (see text also).

substances that stimulate the endings of non-medullated fibres e.g. acetylcholine, nicotine, phenyl diguanide (PAINTAL, 1964, 1971) because their regenerative region (first node) is much less sensitive to drugs than the regenerative region of endings

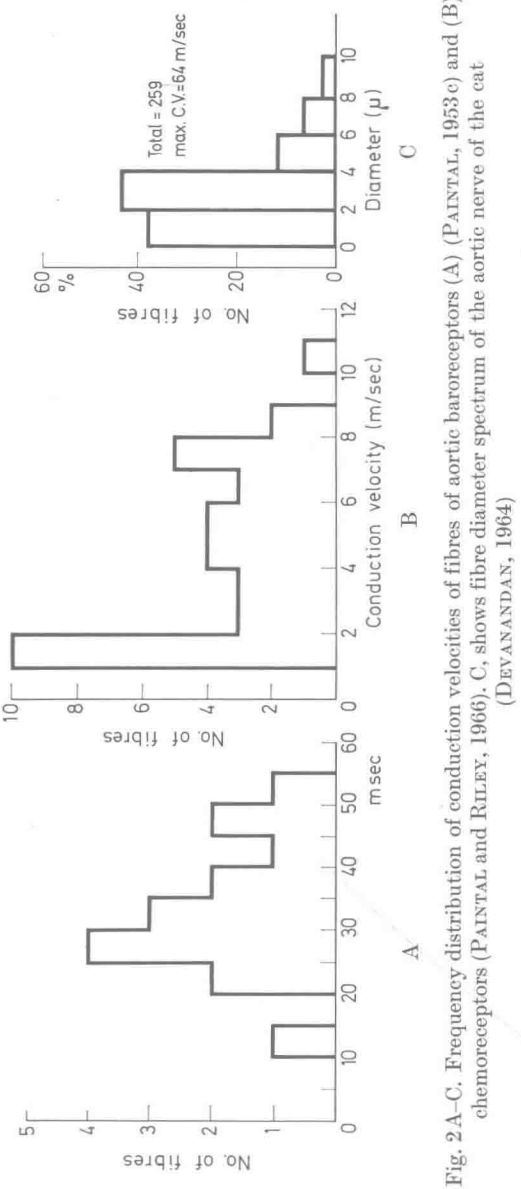

Fig. 2 A–C. Frequency distribution of conduction velocities of fibres of aortic baroreceptors (A) (PAINTAL, 1953c) and (B) chemoreceptors (PAINTAL and RILEY, 1966). C, shows fibre diameter spectrum of the aortic nerve of the cat (DEVANANDAN, 1964)

of non-medullated fibres (Fig. 1B), It is therefore not surprising to find that the carotid baroreceptors with non-medullated fibres and the epicardial endings are the only ones that are stimulated by acetylcholine or nicotine (SLEIGHT and WIDDICOMBE, 1965a; FIDONE and SATO, 1969).

The conduction velocities of cardiovascular afferent fibres are given in Table 1. These are the velocities in the cervical vagus (except in the case of epicardial and pericardial receptors) and in some fibres this velocity remains unchanged right up to the ending (PAINTAL, 1962a). However, in most fibres there is a reduction in conduction rate amounting to 10–40% in the intrathoracic stretch of the nerve fibres and there are a few (say 10%) in which the rate is half that of the velocity of the same fibre in the cervical vagus (PAINTAL, 1962a). These conclusions relate to fibres with conduction velocities greater than 10 m/sec, no information is available regarding slower fibres. However Table 1 indicates that there are likely to be very few medullated fibres with conduction velocities less than 10 m/sec. It is also noteworthy that the conduction velocities of all cardiac fibres (of rhythmically active receptors) ranges from 8 to 29 m/sec and that the mean conduction velocities of all of them is approximately the same.

The distribution of the conduction velocities of fibres of aortic baroreceptors and chemoreceptors and the fibre diameter distribution in the aortic nerve are shown in Fig. 2A–C. If one takes the 3 figures together one finds that the diameter distribution is consistent with the distribution of conduction velocities. Indeed, one can say safely, whether one assumes that the conduction velocity: fibre diameter ratio is 6 (HURSH, 1939) or 5 (BOYD, 1964, 1965), that the fibres below 3 μ in diameter mostly consist of chemoreceptor fibres and those above 3 μ of baroreceptor fibres. DEVANANDAN (1964) found that the conversion factor of 6 fits the electrophysiological data fairly well. Fig. 2A shows that about 20% of the baroreceptor fibres conduct at rates greater than 40 m/sec (corresponding to a fibre diameter greater than 7 or 8 μ). This is a little greater than what one would expect from the results of DEVANANDAN in general although it would fit in with Fig. 2B taken from his paper. The histological observations of SCHMIDT and STROMBERG (1967) on the aortic nerve of swine agree with those of DAVANANDAN (1964). These results therefore clear up certain discrepancies between electrophysiological and histological observations pointed out earlier (PAINTAL, 1963a).

On the other hand in the case of carotid baro- and chemoreceptor fibres of the cat one is forced to conclude from the results of FIDONE and SATO (1969) taken in conjunction with those of EYZAGUIRRE and UCHIZONO (1961) that all the fastest and slowest medullated fibres are chemoreceptor ones and that the baroreceptor fibres conduct only within the range of 15 to 25 m/sec. Clearly this is quite different from what obtains in the case of aortic chemo- and baroreceptor fibres (Fig. 2). The findings of FIDONE and SATO (1969) are also in conflict with those of DE CASTRO (1951) who concluded from his histological findings that all the large and some medium diameter fibres are baroreceptor fibres, the remainder being chemoreceptor fibres. However, it should be pointed out that the results of FIDONE and SATO were obtained using an unusual method of measuring conduction velocities of medullated fibres, i.e. a system of two differential inputs with a common distal electrode so called "monotopic" (see Fig. 1B of their paper). Measurements of conduction velocities of fibres using their technique has yielded values of 20–30 m/sec in non-medullated fibres. And so there is a strong possibility that some of their medullated chemoreceptor fibres were in fact non-medullated (PAINTAL, 1971).

Finally, there is the important finding by FIDONE and SATO (1969) that about 30% of the non-medullated fibres in the carotid nerve are made up of baroreceptor fibres with conduction velocities ranging from 0.5 to 2.0 m/sec.

III. Blocking Temperatures

The relation between diameter of nerve fibres and the temperature at which conduction in them is blocked was discussed in an earlier review (PAINTAL, 1963a). Since then evidence has been obtained to show that all medullated nerve fibres are blocked at about the same temperature i.e. about 7.6°C regardless of their

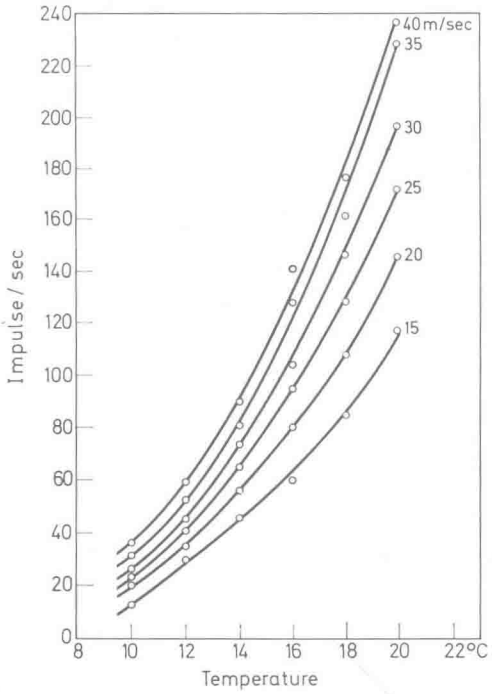

Fig. 3. Maximum transmissible frequency of impulses between 10 and 20°C in fibres with different conduction velocities measured at 37°C (PAINTAL, 1966b)

conduction rates (PAINTAL, 1965a; FRANZ and IGGO, 1968) and so it is not possible to use cold block as a method of blocking the medullated fibres differentially. However it is possible to use low temperatures to reduce the frequency of discharge in nerve fibres since the maximum frequency of impulses that a nerve fibre can conduct varies with the temperature and with its conduction velocity (Fig. 3) (PAINTAL, 1965b, 1966b; FRANZ and IGGO, 1968). It follows that above about 8°C, i.e. above the actual blocking temperature of the nerve fibre, cardiovascular afferent fibres will be able to conduct the first impulse of each burst but the passage of subsequent impulses of the burst will be determined by the temperature of the cold block and the frequency of discharge. Thus the relatively higher fre-

quency of discharges in aortic baroreceptors and type A atrial receptors (PAINTAL, 1953c) would drop out at temperatures which will leave the somewhat lower frequency discharges in some type B atrial receptors largely unaffected. This will explain the observations of TORRANCE and WHITTERIDGE (1948) and WHITTERIDGE (1948) who found that the activity of baroreceptor fibres was blocked at a higher temperature than that needed to block the fibres of atrial type B receptors. It would also be expected that baroreceptor reflexes at low mean blood pressures (e.g. 70 mm Hg) should survive at lower blocking temperatures since the frequency of discharge in the afferent fibres will be lower than normal. Further it should be possible to block practically all impulses of cardiovascular receptors (i.e. baroreceptor, atrial type A and B, ventricular pressure receptors) at about 8° C and leave the impulses of non-medullated chemoreceptor fibres largely unaffected since the frequency of discharge in the latter averages only 9 impulses/sec when they are stimulated during intense hypoxia (PAINTAL, 1967a). At this temperature the relatively high frequency grouped discharges of chemoreceptors will be blocked, but one would not expect the irregularly spaced impulses to be blocked.

Since non-medullated fibres are blocked at a lower temperature than medullated ones (PAINTAL, 1967b; FRANZ and IGGO, 1968) one would expect at least the first impulse of each rhythmic burst to pass through a region of nerve cooled to about 5° C, at which temperature there is total block of conduction in medullated nerve fibres. This would apply particularly to the non-medullated fibres of carotid baroreceptors (SATO *et al.*, 1968; FIDONE and SATO, 1969) and also to the fibres of epicardial receptors (COLERIDGE *et al.*, 1964b; SLEIGHT and WIDDICOMBE, 1965a).

The frequency of discharge produced by excitatory substances e.g. veratridine is relatively high (Figs. 12, 18) (PAINTAL, 1957, 1964). It follows that the discharges so produced by excitatory substances will be blocked at a higher temperature than that needed to block lower frequency natural activity. However, the degree of block will depend on the local experimental conditions and the actual frequency of discharge. Thus under some conditions it is possible for some impulses to pass through a cold block even though the discharge is much above the maximum transmissible frequency. In other cases a steady frequency of discharge only a little higher than the maximum transmissible frequency is completely blocked (PAINTAL, 1965b). This is apparently due to the fact that each impulse arriving at the cooled stretch of nerve produces abortive spikes and although these are of insufficient amplitude for propagation, nevertheless leave behind a refractory period that affects the conduction of subsequent impulses (PAINTAL, 1966a). Such a situation arises from the absolute refractory period being much greater than the absolute refractory period for the initiation of an impulse (ARP_i) at lower temperatures (PAINTAL, 1966a).

IV. Arterial Baroreceptors

A. Carotid Baroreceptors

Of all the cardiovascular receptors, the carotid baroreceptors have been studied most extensively because of the technical advantages available for their study,

namely, easy isolation of the nerve fibres, isolation of the sinus region for perfusion and application of controlled stimuli. As clearly shown by Bronk and Stella (1932, 1935) the carotid baroreceptors are slowly adapting stretch receptors and they therefore respond like the muscle spindle in many ways. Thus the threshold varies from ending to ending, the peak frequency of discharge is attained during the rising phase of the stimulus, there is variable amount of adaptation and there is post-excitatory depression. This particular aspect was studied in more detail by Landgren (1952a) who related it to the dynamic off effect seen in the generator potential of the muscle spindle (Katz, 1950). Bronk and Stella (1935) also found that the activity of the endings was linearly related to blood pressure in many endings until a "saturation" level was reached above which there was no further increase in activity on further increasing the pressure; this pressure level for most receptors was about 140–180 mm Hg. However, there were other receptors in which the ending responded linearly throughout the range of pressure up to 200 mm Hg. These pressures are actually transmural pressures that are responsible for stretching the endings. When the endings are prevented from being stretched by the application of a rigid cast around the artery, they are not stimulated as indicated by the absence of reflex fall in blood pressure on raising the pressure in the carotid sinus (Hauss *et al.*, 1949).

Although it is recognized that the natural stimulus for the carotid baroreceptors is the pulsatile variation in pressure, it has nevertheless been of interest to find out whether a steady pressure is as effective as pulsatile pressure (at the same level of mean pressure) in stimulating baroreceptors and eliciting reflex effects. Ead, Green and Neil (1952) studied this problem systematically and they found that the frequency of discharge during application of steady pressure was less than that attained during pulsatile stimulation. Further, application of pulsatile pressure recruited more units into activity. These results were consistent with their observations on reflex effects of pulsatile and steady pressure.

On application of a rectangular stimulus the frequency of discharge rises to a peak and then falls off to a steady level (Landgren, 1952a) as in the case of the muscle spindle (Matthews, 1931, 1933). The peak frequency of discharge attained in large baroreceptor fibres varies from 250–350 impulses/sec; the maximum adapted frequency varies from 40–70/sec. On the other hand the peak frequency of discharge attained in the case of fibres with small spikes ranges from 50 to 150/sec and the maximum adapted frequency varies from 20–30 impulses/sec (Landgren, 1952a). Such frequencies approximate the maximum frequencies recorded in non-medullated fibres of other sensory receptors e.g. gastric stretch receptors (Paintal, 1954) aortic chemoreceptors (Paintal, 1967a) (see also Paintal, 1964). It is therefore important to consider whether these small-spike fibres were non-medullated since it is now known from the work of Fidone and Sato (1969) that there are many baroreceptors with non-medullated fibres.

Although in a whole nerve that has not been injured (or in thick filaments) it is reasonable to expect that the size of the spikes will vary with the diameter of the fibres (Gasser and Grundfest, 1939), it is important to realise that this relation does not hold consistently in the case of thin filaments. Indeed not infrequently the opposite obtains (Paintal, 1953c) owing to variable experimental conditions, an important variable being injury to nerve fibres, leading to the reduction of the

membrane potential near the recording electrodes. Perhaps in some cases it is this factor that is responsible for the spikes of non-medullated fibres being larger than those of medullated fibres conducting faster than 20 m/sec (Iggo, 1958).

However, even allowing for all these variables it seems reasonable to assume that all the medullated fibres of carotid baroreceptors will have, more or less, the same spike height because according to De Castro's observations one would expect the majority of such fibres to range between 4 to 7 μ in diameter (see

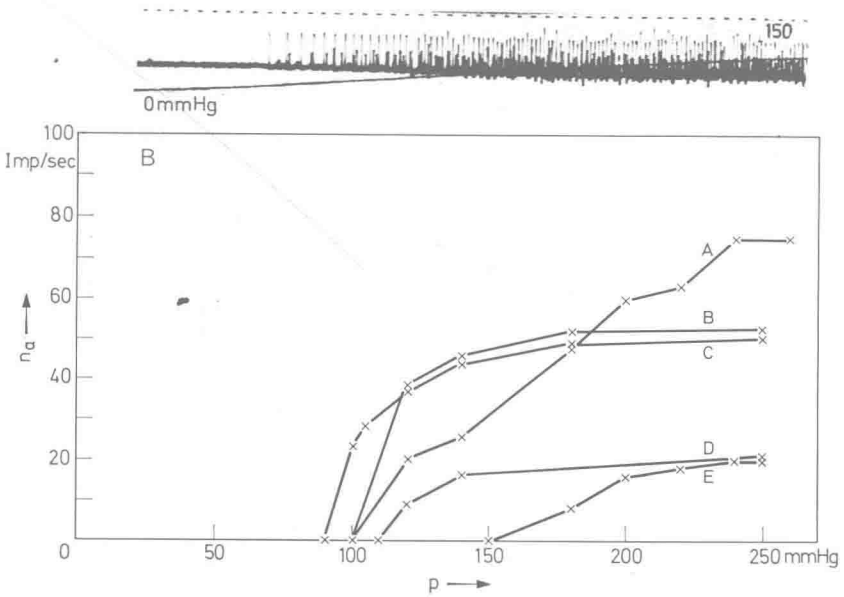

Fig. 4 A and B. Impulses in medullated (large spikes) and presumably non-medullated (small spikes) fibres of carotid baroreceptors produced on raising the pressure in the sinus. B, shows the adapted frequency of discharge (ordinate) in fibres with large, medium and small spikes (presumably non-medullated) at various pressures (abscissa). Note that the frequency of discharge in the non-medullated fibres is much less than that in medullated fibres. (From Landgren, 1952a)

De Castro, 1951). These fibres probably yield the large and medium size spikes. Assuming this to be the case it follows that the small spikes, which are much smaller than the large and medium size spikes (Fig. 4A), can be presumed to originate in non-medullated fibres. In this connection Fidone and Sato (1969) have reported that the baroreceptors with C fibres have a lower frequency of discharge and perhaps a higher threshold than their A fibre counterparts i.e. precisely what Landgren (1952a) found in the case of fibres with small spikes relative to those with large and medium size spikes (Fig. 4B). Thus for the present it would be reasonable to assume that the small spikes recorded by earlier workers (particularly those recorded in the whole nerve e.g. Landgren *et al.*, 1951) arose from non-medullated fibres. These are by far the most numerous (Euler *et al.*, 1941; Landgren *et al.*, 1952; Heymans and Neil, 1958, pp. 28 and 75).

It is now possible to try to reconcile histological observations such as those of De Castro (1928) and Rees (1967) showing that the baroreceptor endings are all located in the adventitia and none in the media on the one hand and those of Landgren *et al.* (1951) and Landgren (1952b) showing that topical application of adrenaline stimulates endings of fibres with small spikes and not those with large spikes on the other. This point has been rather puzzling hitherto (see pp. 73–76 in Heymans and Neil, 1958) because application of adrenaline causes a reduction in the diameter of the vessel and this must presumably reduce the tension in the wall (for the same pressure) in accordance with Laplace's law (see Burton, 1951). As expected the endings with large spike fibres were not stimulated since they are known to lie in the adventitia and hence in parallel with the muscle fibres. On the other hand, the activity of endings with small-spike fibres is increased which implies that such endings must lie in series with the contractile elements. In this connection it is noteworthy that Rees (1967) has found that there are nerve endings in association with smooth muscle cells located in the adventitia of the carotid sinus. In fact some of these presumptive baroreceptor terminals are actually in series with the smooth muscle cells. It is possible that these nerve endings are terminations of non-medullated fibres.

Palme (1943) and Kezdi (1954) observed that stimulation of the local sympathetic branches yields reflex effects typical of baroreceptors. This would fit in with Rees's observation that the smooth muscle cells in the adventitia receive sympathetic nerve endings (Rees, 1967). However Floyd and Neil (1952) could not confirm the observations of Palme. Moreover in agreement with their negative results on reflex effects of sympathetic stimulation they found that stimulation of the local sympathetic branches failed to increase the activity of nearly all the baroreceptor units they tested; only one unit was stimulated. Floyd and Neil (1952) suggested that the effect on carotid baroreceptors could be due to distortion of the sinus region consequent on contraction of the smooth muscle in the adjacent parts of the vessel. The effect of longitudinal tension in the wall of the vessel has also been noted by Angell James (1971) in the case of aortic baroreceptors.

B. Aortic and Brachiocephalic Baroreceptors

The responses of aortic and brachiocephalic baroreceptors are basically similar to those of the carotid ones—the pulsatile discharge being closely related to the aortic pressure curve (Fig. 5) (Whitteridge, 1948; Neil, 1954; Bloor, 1967). The baroreceptors with fibres running in the right aortic nerve of the cat are distributed in several areas of the brachiocephalic trunk (Boss and Green, 1956; Bianconi and Green, 1959a). Those in the arch of the aorta run in the left aortic nerve.

With the chest intact, care has to be exercised in identifying aortic baroreceptors because they could be confused with left atrial type B receptors (Table 3). Such difficulty would not arise if one were to isolate fibres from the aortic nerve in which case one could be more or less confident that one were dealing with aortic baroreceptors. However, when fibres are isolated from the main vagal trunk (Paintal, 1953c) one has to exclude other cardiovascular endings. Table 3 can be of help in identifying easily the different cardiovascular receptors from one