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RECEPTORS SUPPLIED BY SPINAL NERVES WHICH RESPOND TO CARDIOVASCULAR CHANGES AND ADRENALINE

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The well-known arterial baroreceptive afferent fibres pass centrally in the cranial nerves; however, it has been suggested that some afferent fibres of spinal segments may also signal cardiovascular phenomena related to the systemic blood pressure. With one exception, the evidence for such receptors comes from reflex studies. In 1935, Gammon & Bronk reported that a continuous discharge related to static perfusion pressures in the mesenteric arterial system could be obtained from mesenteric Pacinian corpuscles. They also described rhythmic discharges in the splanchnic nerve, presumably from corpuscles, which bore a temporal relation to pulsatile changes of the blood pressure. On the other hand, their conclusions on a baroreceptive role of Pacinian corpuscles are difficult to reconcile with more recent studies which have shown that these receptors are responsive only to mechanical transients (Gray & Matthews, 1951; Gray & Sato, 1953). Even in the reflex studies, the results or interpretations have been inconsistent. Some investigators have reported reflex vasomotor or generalized cardiovascular changes following alteration of the abdominal blood pressure (Heymans, Bouckaert, Farber & Hsu, 1936; Sarnoff & Yamada, 1959), while other workers have been unable to find reflex cardiovascular changes dependent upon baroreceptors in the abdominal region (Gammon & Bronk, 1935; Boyer & Scher, 1960; Heymans, De Schaepdryver & De Vleeschkouwer, 1960). Gruhzit, Freyberger & Moe (1954) have postulated an entirely different type of receptor, one excited by displacements of the thoracic aorta, as the afferent limb for a reflex vasodilatation of the hind limb evoked by injections of adrenaline. The type and characteristics of the receptor responsible for this latter reflex are unknown, although Gruhzit *et al.* (1954) demonstrated that the

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afferent fibres responsible for the effect were present in most of the thoracic segments.

The present study was prompted by the limited or contradictory evidence suggesting that receptors responding to cardiovascular changes reach the central nervous system at spinal levels. Since the previous studies on this question have considered regions supplied by thoracic spinal segments, a systemic survey of afferent fibres entering these levels was made by recording the electrical activity of dorsal root fibres. The stimuli used for the search were the cardiovascular changes induced by intravenous injections of adrenaline or iso-osmotic fluid because it was believed that such changes should reveal either baroreceptive sense organs or the type of receptor proposed by Gruhzit *et al.* (1954). The results show that sense organs with characteristics similar to Pacinian corpuscles do respond to dynamic cardiovascular changes, but not, as originally suggested by Gammon & Bronk (1935), to steady alterations of the mean blood pressure. In addition, suggestive evidence was obtained that intravascularly injected adrenaline may alter the sensitivity of this type of receptor.

METHODS

The described results were obtained from forty-three adult cats sufficiently deeply anaesthetized with Nembutal (sodium pentobarbital, Abbott) to abolish flexion reflexes. The animals were usually also paralysed by Gallamine (Flaxedil, Specia) and artificially respired by a pump through a trachial cannula. Anaesthetic level in paralysed animals was checked by observation of the pupils and by periodically allowing the animal to recover from the neuromuscular blocking agent. A polyethylene cannula was inserted into the left carotid artery to permit recording of the blood pressure with a Statham P-23A pressure transducer whose output was coupled directly to one beam of an oscilloscope. Rectal temperature was maintained between 36 and 39° C.

For the study of dorsal root afferent fibres, the dorsolateral surfaces of five to nine segments of the thoracic spinal cord were exposed to laminectomy. All exposed neural and deep tissues were protected by warm liquid paraffin, equilibrated with 5% CO_2 and 95% O_2, in pools formed by flaps of skin and muscle. Electrical activity of afferent fibres was led off by fine platinum leads and amplified using an amplifier with a short time constant; the resulting discharges were displayed on the other beam of the oscilloscope. Nerves were stimulated electrically by 0·1 msec rectangular pulses. Mechanical stimuli were delivered by a glass rod connected to the moving coil of a Goodman's V-47 electromagnet. The coil was excited either by rectangular pulses or sine waves generated by a beat-frequency oscillator. While energy delivered by the electro-magnetically driven probe was limited at frequencies above 300 c/s, sinusoidal movement to 1000 c/s could be produced at amplitudes above human threshold for vibration.

On occasion the circulating blood volume was expanded by intravenous injections of a gelatin solution (Plasmagel, Bellon) or more transiently with 0·9% NaCl solution. Adrenaline (Adrenalin, Clin-Colmar) solutions were made by diluting a stock solution with 0·9% NaCl solution or modified Locke's solution (without glucose). The intravenously injected quantities of adrenaline gave moderate to marked changes in mean blood pressure and heart rate. In some experiments both cervical vago-sympathetic trunks were cut and in these the circulatory responses to adrenaline and fluid injection differed from the usual preparations. After taking these differences into account, no specific alterations of receptor response were found to be attributable to this manoeuvre.

In order to study the effect of adrenaline injection upon Pacinian corpuscular sensitivity, the abdominal cavity was entered through a lateral incision and the tissue edges were tied to a ring. Mesentery containing a corpuscle judged suitable for study was laid upon a 5 cm diameter plastic plate covered with a thick layer of cork which was rigidly mounted to heavy aluminium animal board. Firm contact between the mesentery and the cork was achieved by wetting it with saline solution and by removing air bubbles through small holes cut in the mesentery. The mesentery surrounding the corpuscle was pinned to the cork in such a way as to avoid interference with its local circulation and flow in nearby vessels. After the corpuscle was in position the abdominal cavity was filled with warm liquid paraffin equilibrated with 5% CO_2 and 95% O_2. Recordings were made from subdivisions of the mesenteric nerve after splitting and selective block of conduction from fibres leading to other receptors so that the activity in the axon from a particular corpuscle could be studied in isolation. Mechanical stimuli (5–10/sec) were provided by small pulsatile movements of a glass rod mounted to a Goodman generator. The stimulating procedure which was found most satisfactory for adjustment of stimulus intensity to near-threshold levels, which would remain constant for some period of time, consisted of placing the glass probe directly upon the cork plate 1–2 mm from the corpuscle being studied. This stimulus was utilized for all the experiments of this type. The stimuli produced by this method were undoubtedly complex, and if well above threshold, resulted in two or three discharges in the axon for each stimulus pulse. With the near-threshold stimuli ordinarily employed, no, or only one, impulse appeared for each mechanical pulse unless the threshold for the corpuscle changed.

RESULTS

Afferent fibres responding to adrenaline injection and blood-pressure changes

In the preliminary experiments, recordings were made from natural bundles of mid-thoracic dorsal roots before, during, and after intravenous injections of small quantities of adrenaline. Such rootlets were subsequently split and the afferent activity of small groups or single fibres was examined following similar adrenaline injections or other stimuli, to study small amplitude potentials (produced by small diameter fibres). It was clear that the majority of dorsal root fibres did not respond regularly to the changes which followed the injection of adrenaline. Cutaneous afferent fibres, with the exception of an occasional 'touch' receptor (Hunt & McIntyre, 1960; Iggo, 1963), did not seem to be affected by adrenaline. These observations led to a concentration upon more deeply located receptors; study of the latter was facilitated by cutting cutaneous and superficial muscular branches of the intercostal nerves near the angle of the rib.

Certain deeply located receptors changed their background discharge after adrenaline injection; however, some of these changes did not appear directly related to adrenaline-caused, generalized circulatory alterations. As an example, discharges from receptors located in the intercostal or vertebral muscle masses were noted to be associated with respiratory movements. A few such afferent fibres temporarily increased their response to respiratory movement after adrenaline injection, but the change was not constant, and other units of the same type were unaffected. It appeared unlikely that this effect represented a signal of cardiovascular alterations since systematic changes in the blood pressure produced by intravenous injections of fluid were completely without effect upon the same afferent fibres. In general, no afferent activity was observed which altered with changes in diastolic pressure unless this was accompanied by changes in pulse pressure.

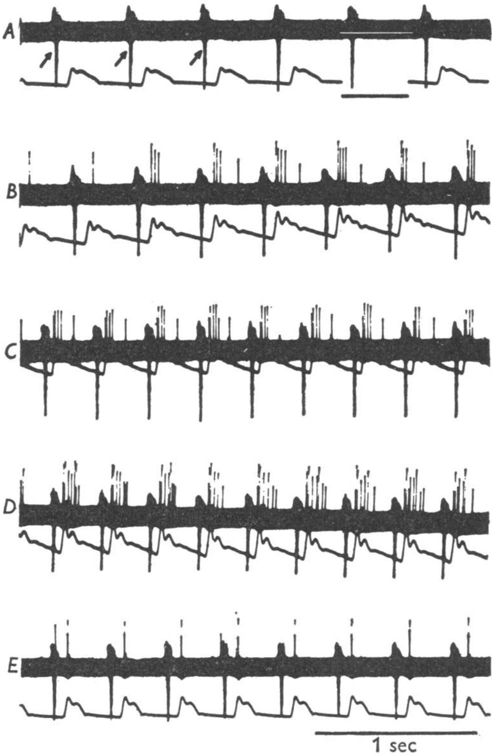

Fig. 1. Discharge in a bundle of thoracic dorsal root fibres after an intravenous injection of adrenaline. Upper trace of each pair is a recording from an undivided rootlet at the T8 level. Lower trace of each pair is left carotid arterial pressure: calibration, 0 and 125 mm of Hg. *A*, control; arrows indicate electrocardiographic artifact; *B*, 8·6 sec; *C*, 20 sec; *D*, 41 sec; *E*, 61 sec after intravenous injection of 10 μg adrenaline. Figs. 2–4 constructed in the same manner.

Receptors discharging in rhythm with the cardiac cycle. Two classes of responses were observed in which one or several impulses occurred with each cardiac cycle. One type was initiated by the thrust of the cardiac apex against the chest wall. This particular kind of response depended on the position of the animal. The afferent fibres excited by heart movement were of several types including cutaneous mechano-receptors and slowly adapting receptors in the intercostal muscle or subcutaneous tissue. Responses to the apical thrust were not seen in experiments in which the superficial and distal branches of the intercostal nerves were cut.

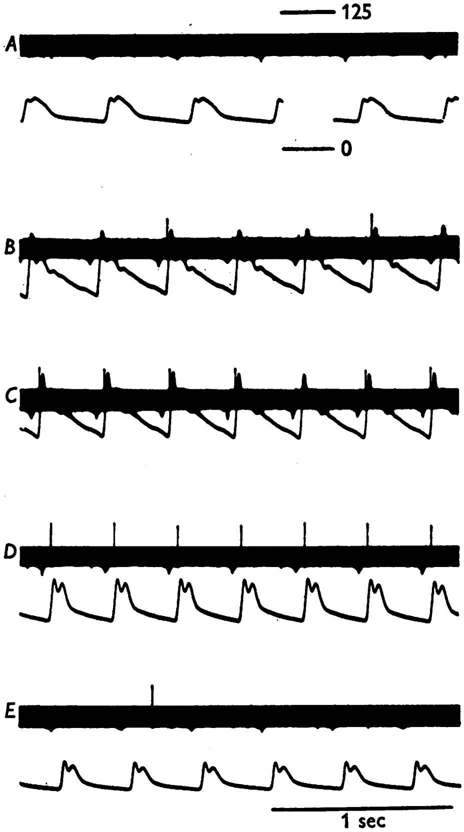

Fig. 2. Response of one element from the group of dorsal root fibres illustrated in Fig. 1. *A*, control; *B*, 20 sec; *C*, 30 sec; *D*, 75 sec; *E*, 100 sec after intravenous injection of 10 μg adrenaline.

The other class of fibres which discharged in association with the cardiac cycle proved to be a more homogeneous group and gave reproducible patterns of response which were largely independent of the position of the animal. Several such units in one dorsal root bundle are illustrated in Fig. 1. At the time of the control record, Fig. 1*A*, the blood pressure of the animal was low and no afferent impulses were recorded. (The deflexion marked by the arrow is an electrocardiographic artifact.) Figures 1*B*–*E* illustrate the sequence of events after an intravenous injection of adrenaline. As the blood pressure increased, one and then a burst of impulses appeared in the dorsal root record, timed to the systolic rise in pressure. In Fig. 1*D*, despite a decrease in diastolic pressure, the rhythmic dorsal root discharge appeared more pronounced. In Fig. 1*E*, the diastolic pressure had fallen to the control level; however, the pulse pressure was still slightly larger than in the control and several fibres continued to be active.

Figure 2 shows the activity of one of the four afferent fibres isolated from the bundle of Fig. 1. The receptor was silent when the diastolic and pulse pressures were low (Fig. 2*A*). In Fig. 2*B*, the pulse and diastolic pressures had markedly increased following adrenaline injection, and the unit discharged in association with the systolic rise in blood pressure in two of the seven cycles illustrated. Approximately 30 sec after the adrenaline injection (Fig. 2*C*) the diastolic and pulse pressures further increased and the fibre discharged more regularly. Still later, Fig. 2*D*, an impulse was associated with each cardiac cycle at the time when the carotid pressures had fallen from the maximum but were still above initial levels.

The timing of the discharge of these receptors suggested that they responded as a consequence of cardiac contraction. Events related to blood pressure or arterial pulsation seemed a possible source of the excitatory stimuli, so a series of observations were made on the association of the afferent impulses to various diastolic and systolic pressures. Figures 3 and 4 illustrate the behaviour of afferent fibres which are representative of the findings. The fibre of Fig. 3 was silent in the control record (*A*) at a carotid pressure of 107/54 mm Hg. A slight increase in diastolic pressure and a more marked increase in the systolic pressure were produced by intravenously injected fluid (Fig. 3*B*) after which the unit occasionally discharged, with the impulse appearing in association with cardiac systole. Adrenaline was injected intravenously shortly before Fig. 3*C* and during the initial rise of pressure no afferent impulses were recorded, but later, a rhythmic discharge became evident. At the time of Fig. 3*D*, the pulse contour and pressure showed a distinct change and one or two discharges appeared with each cardiac cycle. When two discharges were present, the first maintained a temporal relation to the systolic change in carotid pressure. Some 60 sec after the injection of adrenaline (Fig. 3*E*) the unit responded in rhythm to the majority of arterial pulses, even though the diastolic pressure had fallen to a level lower than that of some cycles in Fig. 3*C* which were not associated with impulses. Careful examination of Fig. 3 indicates that the feature of the systemic pressure with which the presence of activity was correlated was the configuration and/or amplitude of the pulse wave. The receptors did not respond to respiratory movements alone, but occasionally a discharge timed to the cardiac cycle would be modulated by respiration as in Fig. 3*F*.

Figure 4 further emphasizes the lack of association of discharge for this type of fibre with the diastolic pressure level. In the control record, Fig. 4*A*, an impulse regularly appeared with each cardiac cycle, yet the diastolic pressure was low (about 30 mm Hg). The diastolic pressure rose markedly 25 sec after the injection of adrenaline (Fig. 4*B*), but the unit discharged less regularly, a situation which became more obvious at the time of Fig. 4*C*. In this animal, as demonstrated by comparing Fig. 4*A* and *C*, the pulse pressure decreased as the diastolic pressure increased after adrenaline injection. As the diastolic pressure fell, the pulse pressure increased, and again there was a regular discharge with each heart beat (Fig. 4*D* and *E*).

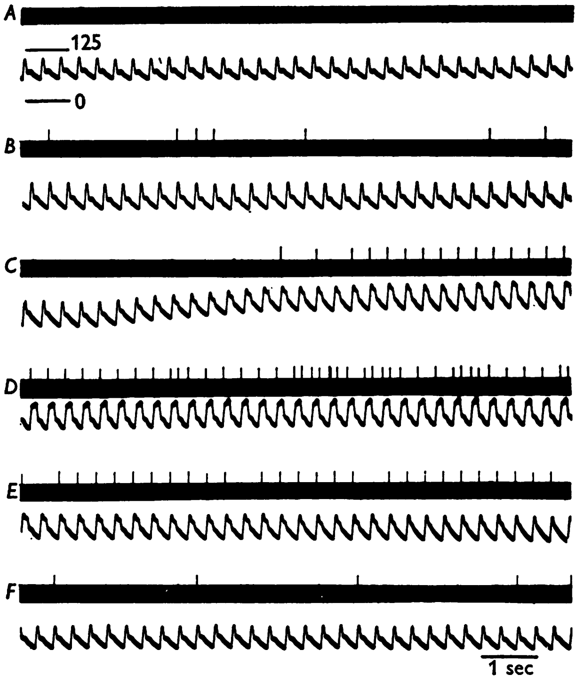

Fig. 3. Discharge of a T 12 afferent fibre during changing circulatory conditions. *A*, control; *B*, after 10 c.c. of Plasmagel injected intravenously; *C*, 10 sec; *D*, 30 sec; *E*, 60 sec; *F*, 150 sec after intravenous injection of 10 μg of adrenaline.

In twenty-seven preparations, over 150 afferent fibres, which discharged in relation to the cardiac cycle in the manner just described, were studied in greater or lesser detail. Neither the level of diastolic nor systolic pressure was signalled by these fibres; but it was consistently observed that any procedure which altered the amplitude and configuration of the carotid pulse wave was associated with a change in their activity. An effective means of initiating or altering their discharge was the intravenous injection of adrenaline; however, intravenous fluid injection also regularly increased the discharge provided that the pulse pressure increased. Conversely, additional anaesthetic agent or 'spontaneous shock' decreased these afferent impulses, if the pulse pressure decreased. Moreover, as Figs. 1, 2 and 3 show, the amplitude of pulse pressure was not the only factor in the relation between the pulse wave and discharge of such receptors, since many would respond at a magnitude of pulse pressure during the later sequence of events produced by adrenaline which was not linked to excitation during the phase of rising blood pressure. In some instances, the shape of the arterial pulse, particularly the rising phase, changed during the course of the adrenaline effects and

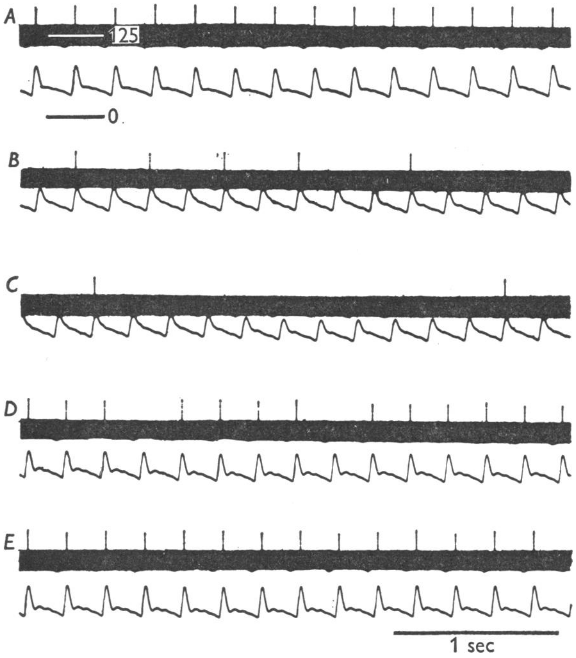

Fig. 4. Discharge of a T7 dorsal root fibre following intravenous injection of adrenaline. *A*, control; *B*, 24 sec; *C*, 36 sec; *D*, 50 sec; *E*, 90 sec after intravenous injection of 10 μg adrenaline. This fibre responded to sinusoidal vibration only when it was applied to a localized point in the 7th or 8th intercostal spaces.

may have contributed to these findings. Another real possibility was that adrenaline had in some way altered receptor responsiveness.

To determine the segmental distribution of fibres with the behaviour described above, each thoracic dorsal root (one or two in a preparation) was systematically examined by recording from very fine filaments. In all segments but T1 and T2, afferent fibres were found which would discharge in association with cardiovascular events as just described. While the relative concentration of fibres in the different segments could not be determined since only one or two levels were studied in a given animal, it was clear that they entered the spinal cord over a large range of dorsal roots and could be readily demonstrated in any dorsal root from T4 to T12.

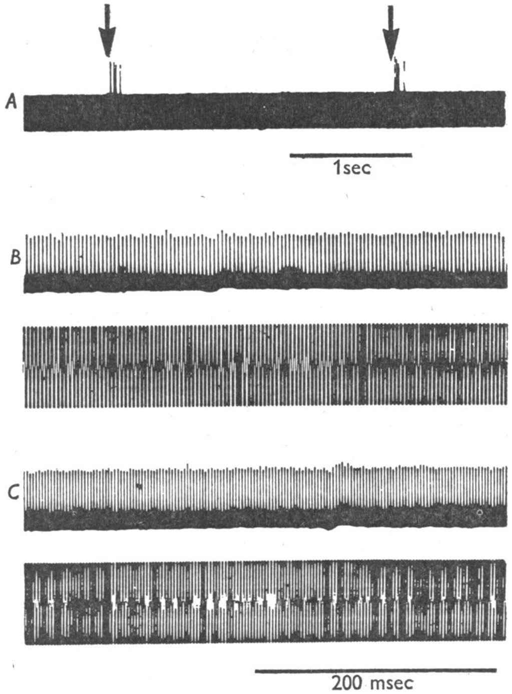

Fig. 5. Response of a T12 afferent fibre to mechanical stimuli. The records were taken from the same fibre whose response is shown in Fig. 3. *A*, with each arrow a sharp tap was delivered to the animal supports. Time calibration shown immediately below the record. *B* and *C* are the response of the unit to sinusoidal vibration applied in the angle between the last rib and the lumbar musculature. Lower traces of *B* and *C* are the vibration frequencies, nominally 300 and 400 c/s, respectively.

Sensitivity to external mechanical stimuli. From the outset it was observed that receptors responding in the manner illustrated by Figs. 1–4 would also respond to external mechanical stimuli. In particular, vibration of the animal or animal supports was especially effective, while slowly applied pressure to various regions was ineffectual. The sensitivity of these receptors to external stimuli varied greatly, some being exquisitely sensitive, while others were relatively insensitive. Quantitative examination of the sensitivity to external mechanical stimuli was not performed, but, in general, units which were active in the absence of adrenaline often were also very sensitive to external mechanical vibration. Figure 5*A* showed the response of the unit illustrated in Fig. 3 to sharp taps to the animal table. A short burst of impulses followed each tap. Vibration applied by an electro-mechanical vibrator was also capable of exciting many of the receptive structures so that they gave one impulse for each cycle of vibration at frequencies between a lower limit of 40 to 60 and an upper limit of 300 to 500 c/s. In Fig. 5*B* and *C*, the response to sinusoidal vibration at approximately 300/sec and 400/sec applied to the angle between the last rib and the lumbar muscles is shown for the fibre of Fig. 3.

The sensitivity to external vibration offered a tool for finding the approximate location of receptors. By adjusting the intensity of mechanical vibration at 200–300/sec to a low value, even the most sensitive receptors proved to have a particular locus at which this stimulus was most effective. Only when the vibration intensity was increased from near-threshold values was it possible to obtain responses from an extensive region. With low-intensity mechanical vibration, the effective region never appeared to be in the skin. For many units the most effective point lay in the region between the vertebral column and the upper abdomen. A number of afferent fibres, particularly those entering the upper thoracic segments, were excited only when the stimulator was placed against portions of the chest. In other cases, the effective locus for near-threshold vibration was in the musculature along the lower lumbar vertebral column or deep within the abdomen. The sensitivity of these receptors to sinusoidal vibration varied as did the sensitivity to jarring of the animal supports: it was impossible consistently to excite certain units, while other units were discharged by vibration intensities close to that of human threshold. The afferent fibres exhibiting lowest threshold to vibration commonly appeared to be located within the abdomen.

Afferent fibres in splanchnic and other deep nerves. Gammon & Bronk (1935) and, subsequently, Gernandt & Zotterman (1943) reported that a number of fibres in the distal end of a cut splanchnic nerve discharged in association with the cardiac rhythm. Recordings were made from the splanchnic nerve to confirm those observations and to compare the behaviour of such splanchnic afferent fibres with the results obtained from the dorsal root fibres. In a typical record, a burst of discharges was recorded from the greater splanchnic nerve with each systolic rise in carotid pressure, and a second burst at the time of the dicrotic notch. When the blood pressure fell after an injection of anaesthetic, or following deterioration of the preparation, the rhythmic discharge from the peripheral end of the cut splanchnic nerve decreased. Conversely, a marked increase in discharge occurred after adrenaline injections. No attempt was made to isolate individual splanchnic nerve elements contributing to this rhythmic discharge; however, as shown below, certain of the afferent fibres studied in the dorsal roots passed through the splanchnic nerves.

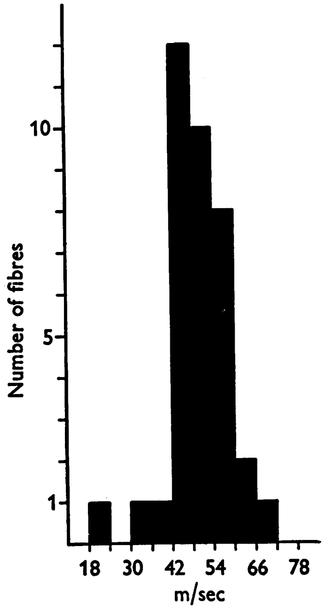

Fig. 6. Conduction velocity measurements for thirty-six dorsal root fibres passing through the splanchnic nerve. Conduction velocity was determined by stimulating the combined splanchnic nerves with 0·1 msec pulses at twice threshold for the fibre to determine the latency of response and by post mortem measurement of conduction distance from the nerve stimulation site to the spinal roots. 0·1 msec was allowed for stimulus utilization at stimulating electrodes. Data collected from seven experiments.

In addition, in several experiments, recordings were made of afferent activity in fine nerves which ran through the lumbar retroperitoneal space. Traced peripherally, these nerves were found to innervate the retroperitoneal fat and connective tissue; they entered the central nervous system through the lumbar sympathetic trunk or the lumbar spinal nerves. Some of these nerves were found to contain one, or a few, afferent fibres which responded to both cardiovascular changes and to mechanical stimulation in the same manner as those studied in the dorsal roots.

The conduction velocity of some individual afferent fibres in the dorsal roots was measured by stimulating electrically the greater and lesser splanchnic nerves at the level of the coeliac ganglion. Conduction distances were measured by post mortem dissection. Conduction velocity was calculated from the latency of response after deducting 0·1 msec as stimulation utilization time. The results of determinations on thirty-six dorsal root fibres studied in seven animals are shown in Fig. 6. Thirty-three of these fibres conducted between 42 and 60/sec, and three conducted between 18 and 42/sec.

The fibres making up this population were found in two ways, about one half with each technique. In the first, units were chosen by their response to adrenaline injection and mechanical stimuli. Then, the splanchnic nerves were stimulated. On the basis of the response to splanchnic-nerve stimulation certain fibres were shown to run in the splanchnic nerve, while others, even from the same segment, were apparently distributed peripherally by other nerves. In particular, fibres of the upper thoracic segments (T3, T4, T5) were not excited by splanchnic nerve stimulation. In the second method, the splanchnic nerves were stimulated and afferent fibres which responded were prepared for individual study and tested for response to circulatory and mechanical stimuli. With the second technique, fibres with conduction velocity of 10–80/sec were identified. Of the fibres identified first by splanchnic-nerve stimulation, some of those conducting over 30 m/sec and all conducting under 15 m/sec would not discharge in association with cardiac events after adrenaline.

The experiments on the deep nerves further documented the fact that the receptors under consideration were widely distributed. In addition, the results establish that some of the responses originated from receptors with splanchnic afferent fibres, but that these represented only a portion of the dorsal root fibres giving rise to discharges associated with the cardiac cycle.

Adrenaline effects upon receptor sensitivity

The particular effectiveness of adrenaline-induced cardiovascular changes in exciting the type of receptors described above, and the time course of the response following intravenous adrenaline injections suggested consideration of the possibility that adrenaline may have altered the sensitivity of the receptor. Some clues as to the nature of the receptors responsible for the rhythmic discharge in the dorsal roots in association with the cardiac cycle appeared in their sensitivity to sinusoidal vibration.

Several investigations have shown that Pacinian corpuscles are particularly responsive to rapidly changing transients and can follow in a one-impulse-for-one-cycle of sinusoidal vibration in the frequency range between 60 and 700 or 800/sec (Gray & Matthews, 1951; Sato, 1961). Certain of the dorsal root fibres responding to cardiovascular changes were shown to pass through the splanchnic nerve and this nerve is known to contain afferent fibres from mesenteric Pacinian corpuscles (Gammon & Bronk, 1935; Gernandt & Zotterman, 1943). Finally, some of the receptors, as judged by their response to near-threshold sinusoidal vibration, were apparently located within the abdomen. For this reason it seemed reasonable to suspect that some of the discharges studied did arise from structures similar to Pacinian corpuscle and that mesenteric Pacinian corpuscles would represent an appropriate receptor on which to test the effects of intravenous injections of adrenaline.

The location and distribution of mesenteric Pacinian corpuscles is such that it is possible to study the conducted activity in the axons from individual corpuscles while the circulation to a corpuscle remains intact. With the technique described in the methods section, corpuscles were prepared for study by being mounted upon a dissecting plate. A corpuscle so mounted was silent provided the supporting structures did not vibrate. Most of the corpuscles studied were adjacent to a mesenteric artery, but the arterial pulsation did not excite the receptor despite its disturbance of the surrounding tissue with each cardiac cycle. This observation was particularly interesting because under the dissecting microscope it could be seen that the smaller mesenteric arteries located near to a corpuscle underwent rather slow changes in shape with each pulse wave, quite in contrast with that which would be observed from large vessels such as the aorta. Discharge of corpuscles selected for study could regularly be evoked by vibrations of the dissecting plate or by movement of a fine probe over the surface of the nearby mesentery.

To test for changes in sensitivity of such corpuscles with a relatively undisturbed vascular supply, a stimulating mechanical pulse was adjusted in amplitude so that the receptor responded to 10–30 % of the applied stimuli. In the best preparations, a relatively constant response could be obtained provided that the number of impulses was averaged for 5–10 sec periods. Presumably, in shorter periods, subthreshold tremors of the apparatus, from external or intrinsic mechanical changes, introduced sufficient variation so as to produce fluctuations in the receptor response. Following establishment of a base-line level of discharge, 10–20 μg of adrenaline was injected intravenously during the course of a photographic record. The latency between the mechanical pulse and discharges in the axon varied only slightly and, following adrenaline, no temporal relation between carotid arterial pulsation and the receptor discharge appeared (Figs. 7 and 8). Figure 7*A* shows the discharge during a control period. Figures 7*B*–*E* are sample records obtained following the intravenous injection of adrenaline and indicate the marked increase in discharge to the standardized excitatory stimulus, an increased responsiveness which occurred roughly in parallel with the maximum change in the blood pressure. Similar results from two other preparations are plotted in Fig. 8.

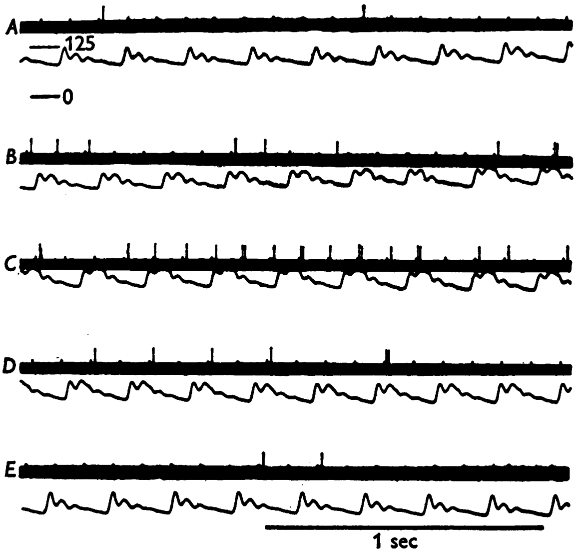

Fig. 7. The effect of an intravenous injection of adrenaline on the responsiveness of a Pacinian corpuscle. Upper trace recorded from mesenteric nerve subdivision. Small deflexions in upper trace are mechanical stimulus artifacts; large deflexions are impulses in the axon from the corpuscle. Lower trace, left carotid arterial pressure (calibration in mm/Hg). *A*, control; *B*, 15 sec; *C*, 23 sec; *D*, 38 sec; *E*, 65 sec after intravenous injection of 20 μg of adrenaline.

The apparent temporal association between changes in the systemic circulation and the responsiveness of a Pacinian corpuscle following intravenous adrenaline, raised the question of whether the altered responsiveness was indirectly produced by a change in the general circulation or whether adrenaline had directly affected receptor sensitivity. To examine this point, a series of experiments was performed on the effects produced by altering the local circulation to a Pacinian corpuscle and by close arterial injection of small quantities of adrenaline. The general experimental arrangement was similar to those used for Figs. 7 and 8 except that a fine catheter was inserted into the mesenteric arterial branch supplying the immediate region surrounding the test corpuscle.

The central portion of the mesenteric-artery branch was ligated; however, the extensive collateral circulation of the region maintained blood flow in the vessels leading directly to the corpuscle. In several preparations, injection of 0·1 or 0·2 ml. of isotonic solution was followed by a period of increased responsiveness of the corpuscle to a constant, near-threshold, mechanical stimulation. In these cases, the pressure in the distal arterial segments had been increased by the injection as is shown by increases in the diameter of the vessel. On the other hand, if the circulation to the small vessels supplying the corpuscle was occluded by ligatures or by clotting, the responsiveness of corpuscles usually decreased.

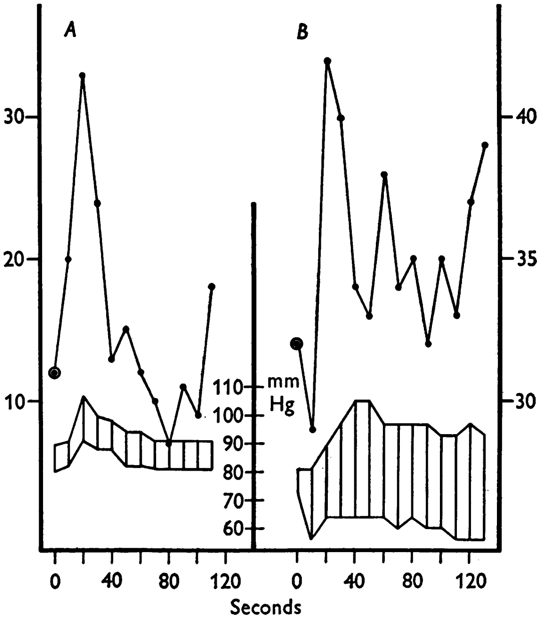

Fig. 8. Responsiveness of two Pacinian corpuscles studied in different animals following intravenous injections of adrenaline. Each filled circle shows total number of impulses recorded from the axon of one corpuscle during a 10 sec period in response to a mechanical stimulus repeated approximately 10/sec. Vertical lines give the carotid diastolic and systolic pressure at the end of each period. Ordinate scale on the left refers to *A*, and that on the right to *B*. Blood pressure scale is on the line separating *A* and *B*. Points marked by a filled circle surrounded by an open circle give response of the fibre during a control period preceding 20 μg of adrenaline injected at zero time.

Selection of corpuscles which lay along a stretch of mesenteric artery with major branches distal to the fine arteriole that supplied the corpuscle reduced, in some cases, the effects of the injection of control solutions into the distal artery. Figures 9 and 10 summarize three sets of observations on three different corpuscles selected in this manner. Figure 9 shows sample records from an experiment contrasting the effect produced by close arterial injection (into mesenteric artery division supplying the region) of 0·2 ml. of modified Locke's solution (Fig. 9*B*, *C*) to that produced by the same quantity of Locke's solution containing 0·2 μg of adrenaline (Fig. 9*E–H*). After the injection of the adrenaline-containing solution (Fig. 9*E–H*), a period of marked increased responsiveness to the mechanical pulse occurred. Similar results obtained on two corpuscles from another animal are shown in Fig. 10. The diagram on the right of Fig. 10*A* schematically represents the anatomical relation of the two

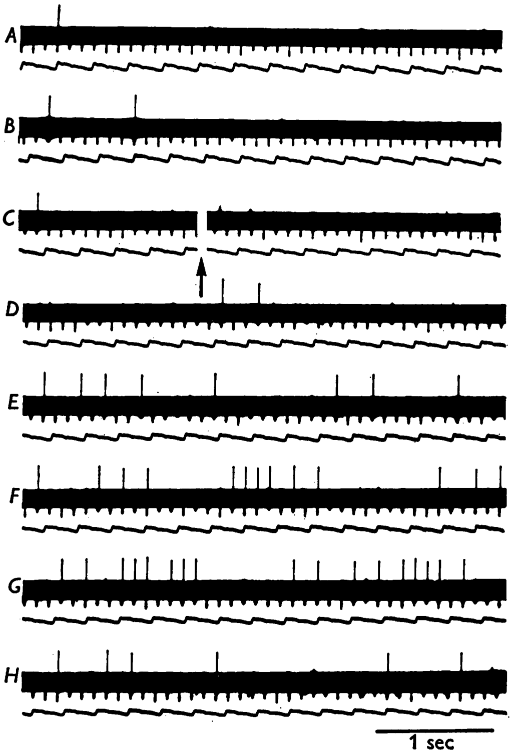

Fig. 9. Effects of close arterial injections on responsiveness of a Pacinian corpuscle. Upper trace of each pair: from subdivision of a mesenteric nerve. Small downward deflexions in this trace are artifacts caused by the mechanical stimulation; upward deflexions are impulses in the axon from the corpuscle. Lower trace of each pair: left carotid arterial pressure. *A*, control. *B*, immediately after end of injection of 0·2 c.c. of 0·9 % NaCl solution. *C*, 40 sec after end of NaCl solution injection. Arrow indicates 30 sec break in record. *D*, continuation of *C*. *E*, 5 sec; *F*, 35 sec; *G*, 65 sec; *H*, 135 sec after injection of 0·2 c.c. NaCl solution (0·9 %) containing 0·2 μg adrenaline.

receptors. The small vessels leading to the corpuscle *A* became occluded after three test injections and a fourth trial revealed no changes in the discharge after injection of either isotonic solution or adrenaline-containing solution. Recording electrodes were then transferred to the branch of the nerve containing the axon from corpuscle *B* and similar tests were performed. One trial is illustrated in Fig. 10*B*; the results once again indicate that enhanced responsiveness followed the injection of adrenaline solution, while isotonic solution alone was associated with little effect.

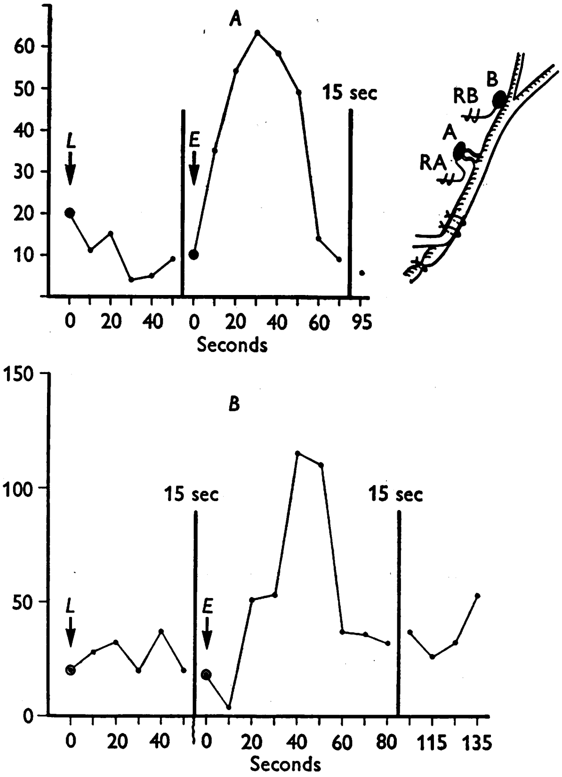

Fig. 10. Responsiveness of two Pacinian corpuscles from the same animal following close arterial injections. Diagram of the anatomical situation is shown on the right of *A*. The graph in *A* is constructed from corpuscle *A*'s activity recorded at RA, and the graph *B* from the corpuscle *B*'s activity recorded at RB. Each plotted point is the number of impulses for the 10 sec period indicated on the ordinate. Injection of 0·2 c.c. Locke's solution (without glucose) is marked by *L*. A filled circle surrounded by an open circle gives the response for the period before the injection. At *E*, 0·2 c.c. Locke's solution containing 0·2 μg adrenaline was injected. The vertical bars within each graph represent 15 sec breaks in the record. See text for additional details.

DISCUSSION

The present experiments demonstrate that a group of afferent fibres entering thoracic levels of the spinal cord discharge in association with cardiac systole, particularly after the intravenous injection of adrenaline. These afferent fibres were found to arise from deeply located mechanoreceptors. An increase in the amplitude of the pulse pressure was found to be accompanied by a response of more such fibres and vice versa. In this sense, the afferent messages carried by such fibres have the qualitative relation to stimulus parameters common to many sense organs. It was also clear that the receptors involved were not sensitive to changes of the mean arterial pressure alone. The final mechanical event responsible for the cardiac-linked discharge was not determined; however, it appeared likely that mechanical transients produced by pulsation of larger arteries were the effective source of excitation. This conclusion was reached on several grounds: the receptors were shown to have greatest sensitivity to mechanical stimuli in specific regions and presumably were located in the vicinity of such loci; the sensitive loci were widely distributed in the abdominal, lumbar and thoracic regions; the receptors were relatively insensitive to slowly occurring mechanical changes but sensitive to rapid mechanical transients. The latter observation would rule out relatively low-frequency ballistic changes of the type contributing to the ballistocardiogram.

The mechanical sensitivity of the receptors producing the rhythmic afferent discharge in association with the cardiac cycle resembled Pacinian corpuscles in their response to mechanical transients and sinusoidal vibration at frequencies above 250 c/s. The passage of some of the afferent fibres through the splanchnic nerves also pointed to Pacinian corpuscles, since it has been shown that discharges in the splanchnic nerve occurring with the heart beat come from Pacinian corpuscles of the mesentery (Gammon & Bronk, 1935; Gernandt & Zotterman, 1943). On the other hand, a number of the elements sensitive to pulsatile features of the blood pressure were located somewhere in the thorax, a region where large Pacinian corpuscles are not common. Also, the conduction velocity of those afferent fibres shown to pass through the splanchnic nerves was lower than a group of Pacinian corpuscles of the cat's hind limb (Hunt & McIntyre, 1960; Hunt, 1961), with generally similar properties. Thus, it is likely that some of the afferent fibres studied originated from receptors other than the large Pacinian corpuscle, perhaps from structures such as the paciniform receptor which are morphologically very similar to the Pacinian corpuscle. Paciniform receptors are smaller than the large corpuscle, have a wide distribution, are common in the tissue of the intercostal space (Barker, 1962), and respond solely to transients (Boyd, 1954).

The experiments on mesenteric Pacinian corpuscles lead to the conclusion that this receptor increases in sensitivity following intravascular injections of adrenaline. In the case of intravenous injections of adrenaline, the changes in the systemic circulation may have caused generalized alterations of some sort (such as in the extracellular fluid content of the supporting tissue) which, in turn, may then have changed the relation between the sense organ and the excitatory stimulus. The fact that similar changes in responsiveness followed close arterial injections of adrenaline would tend to indicate that the changes in responsiveness after intravenous injections were not due solely to such complex factors related to the general circulation. One conceivable source of changes in sensitivity of a corpuscle following close arterial injection was an alteration in local circulation to the sense organ, since it was found that interruption of this circulation was followed by an increase in threshold, while increased pressure in the mesenteric artery of the region was often associated with a decrease in threshold. It was also noted that a temporal relation existed between changes in the adrenaline-induced systemic blood pressure and the enhanced corpuscular responsiveness. Other mechanoreceptors have been described which change sensitivity owing to alterations in local circulation following sympathetic stimulation or adrenaline injection (Eldred, Schnitzlein & Buchwald, 1960) or after sympathetic stimulation or local application of adrenaline in the absence of circulation (Loewenstein, 1956; Loewenstein & Altamirano-Orrego, 1956; Hunt, 1960). In any case, it seems likely that the response pattern noted in the dorsal root fibres following intravenous injections of adrenaline was partially the result of changes in sense-organ sensitivity to the effective stimulus.

The present experiments offer no evidence as to the possible functional significance of the receptors discharging in association with cardiac systole. It seems unlikely, in view of their wide-spread distribution and relative commonness, that the response to cardiovascular events is purely an incidental event. This would be particularly true for the receptors relatively insensitive to externally produced mechanical vibration. Cells of nuclei belonging to ascending sensory pathways have been observed which are active in synchrony with the cardiac cycle and whose general characteristics suggest that they might be excited by the afferent fibres of the type described herein (Perl, Whitlock & Gentry, 1962; Andersson, 1962; G. Gordon, personal communication). The possibility exists also that such receptors might have a role in the regulation of circulation. Gruhzit *et al.* (1954) found, in a detailed series of experiments on the dog, that increased blood flow to the hind limb could be evoked by injections of adrenaline, and that the effect was a reflex dependent upon receptors whose afferent fibres entered the thoracic dorsal roots. The maximum reflex effect in their experiments (Gruhzit *et al.* 1954) required that a positive inotropic effect was produced upon the heart and that adrenaline reached the descending thoracic aorta. The effective excitatory stimulus for the reflex was shown to be a mechanical transient and the receptors were believed to be distributed along the thoracic aorta. On the basis of these experiments by Gruhzit *et al.* (1954) it appears that sense organs with afferent fibres entering the spinal cord may reflexly assist in the re-distribution of blood when the circulation is under strong sympathetic excitation. If mechanoreceptors which can become rhythmically active with the cardiac cycle do contribute to cardiovascular reflexes, then certain previous studies on the influence of spinal afferent fibres in cardiovascular control may have given negative or conflicting results for several reasons. In general, the stimuli used in such studies were changes in the mean blood pressure (Boyer & Scher, 1960; Heymans *et al.* 1960; Sarnoff & Yamada, 1959), yet none of the receptors observed in the survey conducted as part of the present investigation were capable of signalling changes in mean blood pressure. Furthermore, these previous studies judged cardiovascular effects by changes in the systemic pressure. Cardiovascular reflexes dependent upon spinal afferent fibres may be involved only in the re-distribution of blood as part of a mechanism similar to that described by Gruhzit *et al.* (1954) without necessarily altering systemic blood pressure.

SUMMARY

1. In cat a search was made for receptors responsive to circulatory changes by recording electrical activity from small bundles of thoracic dorsal fibres and testing with intravenous injections of adrenaline.

2. In each dorsal root from T3 to T12, some fibres discharged in rhythm with the cardiac cycle. Changes in diastolic or mean blood pressure were not signalled by such fibres, but they altered response following variations in the amplitude and configuration of the pulse wave. The same afferent fibres responded to mechanical transients and sinusoidal vibration (50–500 c/s). Low-intensity external stimuli were effective at particular loci in the abdomen or chest. Some, but not all, of this group of fibres passed through the splanchnic nerves. The conduction velocity of thirty-six fibres of those responding to splanchnic-nerve stimulation ranged from 18 to 66 m/sec with a peak at 45 m/sec. It was concluded that the response in association with the cardiac cycle was initiated by a mechanical transient related to the pulse wave in larger blood vessels and came from receptors similar to Pacinian or paciniform corpuscles.

3. The particular effectiveness and time course of responses after intravenous adrenaline suggested possible sensitization of the receptors by this substance. In a separate series of experiments, the responsiveness of single mesenteric Pacinian corpuscles to a constant mechanical stimulus was shown to be changed by alteration of the local circulation to the receptor. Intravenous (10–20 μg) and close arterial (0·1–0·2 μg) injections of adrenaline solutions were followed by enhanced responsiveness of Pacinian corpuscles to testing mechanical stimuli.

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