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CHAPTER 7

Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception

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Introduction

Organs in the abdominal and pelvic cavities have a dual extrinsic afferent innervation which travels to the central nervous system in the autonomic nerve trunks; the cell bodies of afferents that run with the parasympathetic fibres are concentrated in the vagal nodose ganglia and in the sacral dorsal root ganglia, whereas those of afferents in the main sympathetic nerve trunks have a thoraco-lumbar distribution. Both sets of visceral afferents participate in a number of reflexes and in visceral sensations. Noxious sensations from viscera probably depend mainly on spinal visceral afferents that enter thoraco-lumbar and sacral segments of the cord. The stimuli that elicit these sensations include excessive distension and contraction of hollow viscera, traction on mesenteries, and inflammation or chemical stimuli within the peritoneal cavity.

Many vagal afferent neurones from the gastrointestinal tract react quite selectively to mechanical stimuli to the mucosa or muscle, and to chemicals within the lumen, and can be divided into separate populations with different functional properties (Leek, 1977; Mei, 1983, 1985).

This may apply also to some spinal visceral afferent neurones (Mei, 1983). However, for the majority of spinal visceral afferents, it is not at all clear whether they can be excited specifically by a particular physical or chemical stimulus, and whether the excitation of these afferents is linked more or less selectively to one visceral sensation or reflex. Certain sacral visceral afferents may be involved in maintaining continence and/or in emptying of the urinary bladder or the colon; whether these afferents are also specifically linked to the corresponding sensations during micturition or defaecation, and to other sensations, such as pain, is unknown. For example, it is known that slow passive distension of the urinary bladder can elicit a variety of vague sensations in humans that span from feelings of slight pressure "deep in the mid-perineum or faint pressure from within" to fullness and then to pain (Denny-Brown and Robertson, 1933). These and other sensations from the urinary bladder can probably be elicited from the sacral afferents as well as hypogastric afferents (Riddoch, 1921; Denny-Brown and Robertson, 1933; White and Sweet, 1969).

Are the different qualities of sensation that originate from one viscus elicited by the excitation of different types of afferents, or are they all subserved by a single category of afferents? This important question leads to one of the main problems we will deal with in this review: to what extent can spinal visceral afferents from abdominal and pelvic organs be excited specifically by one or a few of the types of mechanical or chemical stimuli that can occur in the visceral domain?

Theoretically, there are several ways in which

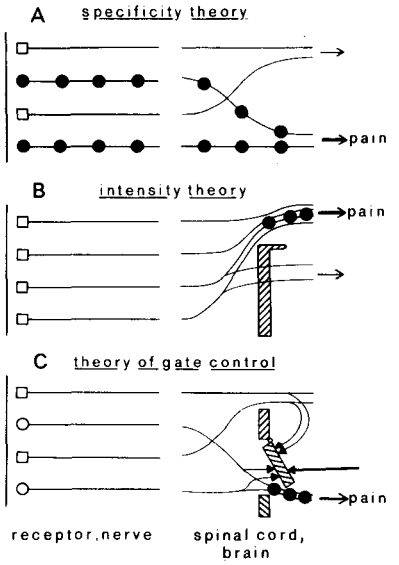

Fig. 1. Schematic representation of theories of neuronal encoding of peripheral events which lead to pain. A. The "specificity theory" postulates specific nociceptive primary afferent neurones which synapse specifically with second-order neurones, etc., thus establishing nociceptive pathways from the periphery to the cortex. B. The intensity theory is based on the assumption that nocuous and non-nocuous peripheral events are encoded in the intensity of the discharge of the same population of primary afferent neurones. Pain appears when the intensity of the discharge reaches a certain height; this theory postulates a central "pain threshold". C. "Theories of gate control" have their origin in the "pattern theory", which assumed that nocuous and non-nocuous events are encoded by different patterns of discharge in the same population of primary afferent neurones. The gate control in its modern form postulates that the event "pain" is the result of the balance of the activity in large- and small-diameter afferent fibres and of central impulses which operate at a neuronal gate in the spinal cord or in supraspinal brain structures. The gate control is principally compatible with the stimulus specificity of the primary afferent neurones. Modified from Handwerker (1984). For details, see text.

different peripheral stimuli in the visceral domain could be encoded by primary afferent and central neurones so as to elicit different sensations: (1) Primary afferents from an organ react specifically to certain stimuli and not to others. These afferents are more or less specifically linked synaptically to neurones in the spinal cord and lead, when excited, to characteristic sensations and reflexes (Fig. 1A). This is the simplest theory and can be traced back to Johannes Müller and Max von Frey (see Sinclair, 1981). The specificity theory is compatible with the idea of an "adequate stimulus", i.e., "that the sensorial end-organ is an apparatus by which an afferent nerve fibre is rendered distinctly amenable to some particular physical agent, and at the same time rendered less amenable to other excitants ..." (Sherrington, 1900, 1906). It is generally — though not universally — believed that this theory applies to the cutaneous sensations (Burgess and Perl, 1973; Lynn, 1984; Perl, 1984). (2) Primary afferents from an organ encode the peripheral stimuli that can elicit various sensations and reflexes in the intensity of their discharge. In this case, one must assume that the major decoding process leading to different sensations, including visceral pain, occurs centrally, e.g., by way of a central threshold. This theory is called the "intensity theory" or "summation hypothesis" (see Fig. 1B) and was particularly propagated by the German clinician Goldscheider (1920), the great opponent of von Frey, and some physiologists believe it to apply to visceral sensations (Morrison, 1977, 1981; Malliani and Lombardi, 1982). (3) The third theory, which was created in the first half of this century and particularly favoured by psychologists, is the "pattern theory" (Nafe, 1929; see Kenshalo, 1984). In its original, extreme form this theory postulated that sensations result from different spatio-temporally dispersed patterns of afferent discharges, and that there is no stimulus specificity of these afferents at all. This theory did not survive since ample evidence had accumulated proving the existence of many afferents which were stimulus-specific, particularly in skin. Whether or not it is also valid for the spinal afferent innervation of viscera and deep somatic tissues (Mense, 1985) is a matter of debate. In a modern form, the "pattern theory" reappeared in the "gate control theory" of pain by Melzack and Wall (1965). This theory states that the discharges in small myelinated and unmyelinated fibres converge on second-order neurones in the dorsal horn of the spinal cord, and that pain results, depending on the balance of excitation in small- and large-diameter

fibres, keeping a hypothetical neuronal gate in the spinal cord open by activity in small-diameter fibres (allowing pain to appear) and closed by activity in large-diameter fibres or by central impulses. This theory is also compatible with the stimulus-specificity theory of primary afferents (Fig. 1C); however, scientifically it can barely be proved or disproved. In this sense, its value is more heuristical, as it initiated a large body of experimental work (for discussion see Nathan, 1976; Wall, 1978; Sinclair, 1981).

This review focusses on the functional properties of spinal afferent neurones supplying abdominal and pelvic viscera and, in particular, on the problem of how physical and chemical stimuli that lead to visceral pain in humans and equivalent reactions in animals are encoded. Data obtained on spinal visceral afferents from various organs in animals, using neurophysiological and morphological techniques, will be discussed and compared with information obtained from the literature concerning the conditions which evoke visceral sensations and reflexes in humans. Finally, the whole complex will be discussed in the framework of the theories outlined above, in order to get some idea of the possible ways in which the peripheral events in the visceral organs are encoded in the discharge of visceral afferents.

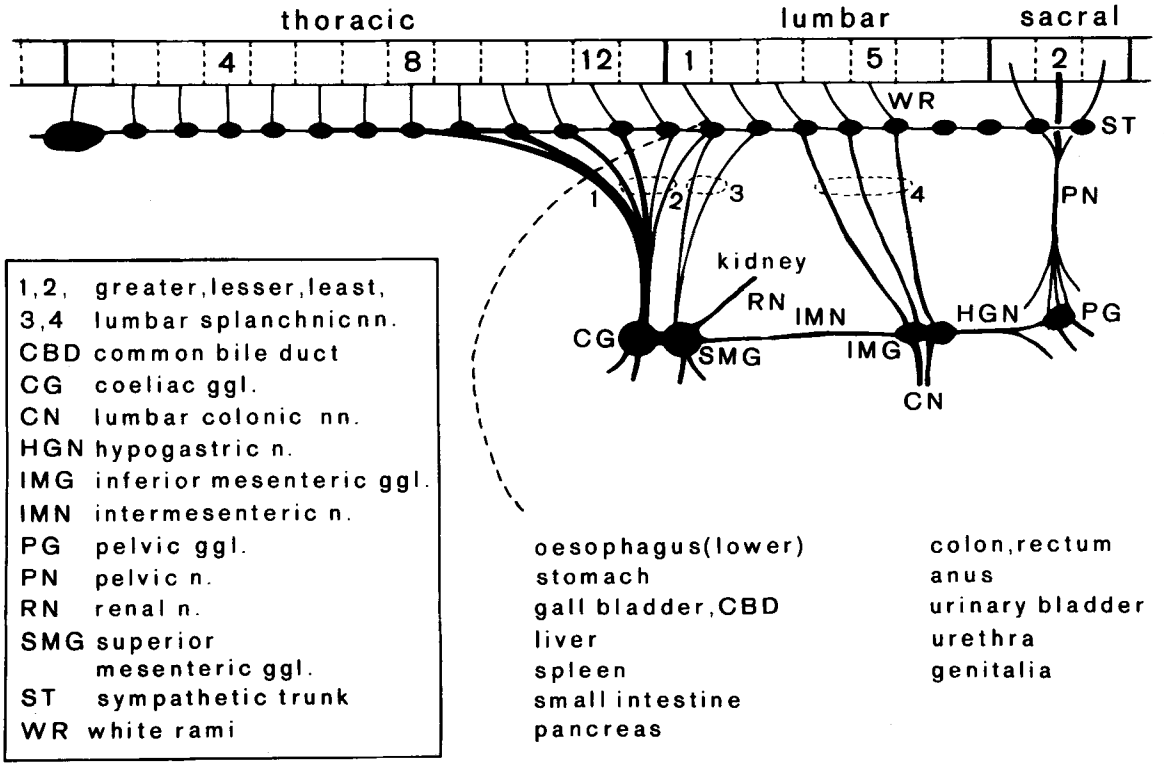

Fig. 2. Schematic arrangement of visceral nerves in the cat which contain spinal afferent fibres from abdominal and pelvic organs. Sympathetic trunk (ST) and white rami (WR) are indicated. There are only a very few pelvic afferent fibres which travel through the sympathetic trunks and have their cell bodies in the dorsal root ganglia rostral to L7. Most electrophysiological and morphological studies reported in this review were conducted on afferents running in these nerves. The diaphragm is indicated by the interrupted line. The nomenclature greater, lesser, least and lumbar splanchnic nerves (1, 2, 3, 4) is equivalent to the officially accepted anatomical nomenclature N. splanchnicus major, N. splanchnicus minor, N. splanchnicus imus and Nn. splanchnici lumbales. The pelvic nerve is officially named Nn. splanchnici pelvini (Williams and Warwick, 1980).

The methods employed in the morphological and neurophysiological studies on animals and the sensory studies in humans have been described extensively in the literature referred to in this review. Details of procedures will be described if necessary, as results are presented.

Numerical and spatial aspects of the spinal innervation of viscera

Numbers of spinal visceral afferents

The last decade has seen a considerable improvement in the quality and quantity of information available concerning the numbers of afferents that innervate the abdominal and pelvic viscera of the cat (see Fig. 3). Quantitative studies on neuronal somata identified by retrograde tracing methods, particularly the horseradish peroxidase (HRP) technique, and on axons in peripheral nerves using the electron microscope have been largely responsible for this change. The advantage of the HRP technique, when applied to visceral nerves, is that one can obtain with relative ease, in the *same* animal, quantitative estimates of numbers, segmental distributions, dimensions and locations of afferent and pre- and postganglionic neurones projecting in the labelled nerve (e.g., Baron et al., 1985a–d). Electron microscopy is not so easy, but it does allow precise numbers and sizes of axons in peripheral nerves to be obtained. Recent studies on the greater splanchnic nerve, for instance (Kuo et al., 1982), have used more appropriate nerve sections than previously (Foley, 1948; Ranieri et al., 1975) to establish the numbers of afferent preganglionic and postganglionic fibres in this nerve. They estimated a total of 6000–7000 fibres (bilaterally), which included about 600–700 myelinated axons, the largest of which are connected to mesenteric Pacinian corpuscles. Kuo and De Groat (1985), using HRP, found an even lower number of afferent neurons (about 2400, unilaterally) projecting in the left greater splanchnic nerve. This estimate may be too low since it is based on the average of four animals and not on the best preparations; furthermore, the authors may have overcorrected their numbers using Abercrombie's correction (Abercrombie, 1946; cf. McLachlan and Jänig, 1983).

The lesser (or minor) splanchnic nerve is estimated to be approximately half the size of the major splanchnic nerve (Kuntz et al., 1957). No estimate can be made of the number of afferent fibres in the least splanchnic nerves, which originate from the first and second lumbar sympathetic ganglia in the cat. These nerves are about the same size as the lumbar splanchnic nerves (Baron et al., 1985a). Thus, it would not be surprising if they contained another 1000–2000 afferent axons, the majority probably supplying the kidney (Kuo et al., 1983).

The afferent fibre numbers of the hypogastric, lumbar splanchnic, lumbar colonic and pelvic nerves (see Fig. 2) have now been studied adequately, and the lumbar innervation uses about 4600 afferents (Baron et al., 1985b–d) and the sacral innervation about 7350 afferents (Morgan et al., 1981). In total, about 22,000–25,000 primary afferent neurones appear to be responsible for signalling afferent information from the abdominal and pelvic

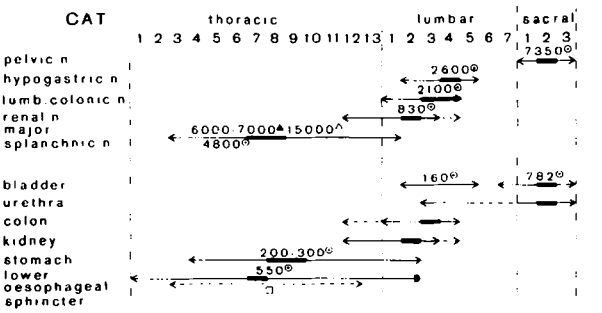

Fig. 3. Segmental distributions and numbers (both sides) of visceral afferent neurones projecting in different visceral nerves and to abdominal and pelvic organs of the cat. For techniques used see inset in Fig. 4. Data from: pelvic n., Morgan et al. (1981); hypogastric n. and lumbar colonic n., Baron et al. (1985b,d); renal n., Kuo et al. (1983); major splanchnic n., Foley (1948), Ranieri et al. (1973, 1975), Kuo et al. (1982), Kuo and De Groat (1985); urinary bladder, Applebaum et al. (1980); urethra, Downie et al. (1984); colon, Hazarika et al. (1964), Baron et al. (1985d); kidney, Kuo et al. (1983); stomach, El-Quazzani (1981, quoted by Cervero et al., 1984); lower oesophageal sphincter, Clerc (1983).

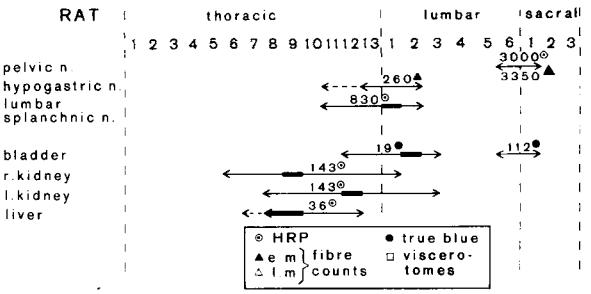

Fig. 4. Segmental distributions and numbers of visceral afferent neurones projecting in different visceral nerves and to abdominal and pelvic organs of the rat. Data from: pelvic n., Hulsebosch and Coggeshall (1982), Nadelhaft and Booth (1984); hypogastric n., Hulsebosch and Coggeshall (1982); lumbar splanchnic n., Neuhuber (1982); urinary bladder, Applebaum et al. (1980), Sharkey et al. (1983); right (r.) kidney, left (l.) kidney, Ciriello and Calaresu (1983); liver, Magni and Carobi (1983).

viscera of the cat. To this number, another 1000 afferents from T1–T7, that innervate the heart, thoracic large vessels and lungs (Oldfield and McLachlan, 1978; Rühle et al., 1985), may be added. In the cat, the estimated total number of spinal visceral afferents is about 1.5–2.5% of the total number of spinal afferent neurones supplying the periphery, which may amount to about 1–1.5 million (Holmes and Davenport, 1940). This low percentage is slightly less than that for individual dorsal root ganglia T8 and T9 (Cervero et al., 1984). The numbers of fibres in the pelvic, lumbar splanchnic and renal nerves of the rat appear to be about 40, 20 and 33%, respectively, of those in the cat (see Fig. 4).

Segmental distribution of spinal visceral afferents

Afferents from different intra-abdominal nerve trunks enter different segments of the cord: there is a degree of overlap between these groups of afferents in the dorsal roots, but each nerve shows a peak of afferent innervation in one or two adjacent segments. For example, Baron et al. (1985b–d) and Kuo et al. (1983) have demonstrated peak innervations from the hypogastric, lumbar colonic and renal nerves in the fourth, third and second lumbar dorsal root ganglia, respectively, while the majority of afferents in the pelvic nerve have cell bodies in the second sacral segment in the cat (Morgan et al., 1981). The segmental innervation of different viscera also shows considerable overlap, as would have been predicted by physiological studies of viscerotomes (Hazarika et al., 1964). However, observations on the numbers of filled cells in dorsal root ganglia following injection of HRP or True Blue into a viscus shows that the innervation of each organ is most dense in only one or two segments; thus, Applebaum et al. (1980) have shown that the bladder afferents enter the cord in greatest numbers through the third lumbar and second sacral dorsal roots in the cat, and the second and sixth lumbar segments in the rat. Sharkey et al. (1983) found peaks at L1 and L6 in the rat using True Blue as a marker. Bladder innervation is thus at a higher segmental level in the rat than in the cat, and, in particular, the majority of pelvic nerve afferents enter the lumbar rather than the sacral cord. In this species the density of the afferent input from the left and right kidneys and the liver/biliary tract is maximal at T12, T9, and T8/T9, respectively, with the liver being represented predominantly on the right side, and the kidneys being innervated unilaterally (Applebaum et al., 1980; Magni and Carobi, 1983; Ciriello and Calaresu, 1983). The liver and biliary tract also have a significant vagal innervation.

Thus, the relationship between a viscus and the spinal cord can be described in terms of the spinal segments that receive the majority of the afferent fibres and the degree of lateralisation of this afferent pathway. True visceral sensation (arising from a viscus without any involvement of the parietal peritoneum) is felt in the midline of the abdomen if the viscus receives a bilateral afferent input of roughly equal size; or to one side of the midline if the viscus is innervated either predominantly or completely from one side of the neuraxis (see Bentley and Smithwick, 1940). Thus, the kidney, gallbladder and ovary are the main abdominal viscera giving true visceral sensations that are lateralised. True visceral sensations from the gut tube and bladder are normally felt in the midline, but there are

reports of localized stimulation within the bladder being lateralised by subjects (Langworthy et al., 1940, p. 129). Applebaum et al. (1980) calculated that less than 10% of afferent fibres from one side of the bladder cross over to the opposite side of the cord, and Baron et al. (1985b) found that approximately 20% of hypogastric nerve afferents do.

Ventral root afferents

There are some reports that unmyelinated afferent fibres exist in the lumbo-sacral ventral roots of cats and that many of these have receptive fields in the viscera (Coggeshall et al., 1974; Applebaum et al., 1976; Clifton et al., 1976; Coggeshall and Ito, 1977). It now appears that few of these enter the spinal cord through the ventral roots; most appear to loop back into the dorsal roots or innervate the pia mater (Risling et al., 1984a), but some have been traced to the dorsal horn (Light and Metz, 1978). There are few reports of functional studies on reflexes induced by "ventral root" afferents. Longhurst et al. (1980) concluded that they have a minor role to play in the hindlimb pressor reflex in cats.

Spinal afferent neurones branching to visceral and somatic tissues

Recently, it has been proposed that some afferent neurones send axon collaterals into two different somatic nerves or into a somatic and a visceral nerve. This idea is supported by some neurophysiological and histological experiments (Bahr et al., 1981; Pierau et al., 1982; Taylor and Pierau, 1982), but the evidence of these groups deals with different neuronal populations. Bahr et al. (1981) studied unmyelinated axons in the lumbar splanchnic nerves of the cat that followed stimuli to the white ramus and to somatic nerves at 50 Hz, and could have been afferent. Antidromic stimulation from the dorsal root was not performed and receptive fields were not located because both visceral and somatic nerves were cut. All of these fibres were unmyelinated, had no ongoing discharge and could not be activated reflexly via spinal or supraspinal pathways. Evidence of branching was present in 18% of 84 unmyelinated afferents studied in the lumbar splanchnic nerves.

In contrast, Pierau et al. (1982) studied intracellular recordings from cells in the L6 dorsal root ganglion of the rat that had evidence of axon collaterals in the sciatic and pudendal nerves. All of these axons were myelinated and the majority conducted at 30–60 m/second. 44% of cells were found to respond to stimulation of both nerves, but high-stimulus voltages were used and it is possible that some stimulus spread may have occurred. A later study by Taylor and Pierau (1982) demonstrated double fluorescence in L6 dorsal root ganglion cells following the application of bisbenzimide or Nuclear Yellow to the pudendal nerve and of propidium iodide or Fast Blue to the sciatic nerve.

Branching of sensory axons distal to sacral dorsal root ganglia in the rat appears to be a relatively common occurrence (Langford and Coggeshall, 1979, 1981). These authors compared the number of dorsal root ganglion cells with the number of fibres in the nerve 0.2 mm distal to the end of the dorsal root ganglion; they found about 2.3 times more axons than dorsal root ganglion cells and concluded that individual sacral primary afferent neurones may send several axons to the periphery. As interesting as these results and the interpretation may appear, it must be kept in mind that the counts were made 5–7 days after cutting the sciatic nerve and the ventral roots and after sympathectomy. These surgical procedures might well have induced regenerative changes (sprouting!) of the primary afferent neurones (Risling et al., 1983, 1984b). Unfortunately, no control data (obtained on rats without surgery) have been reported by Langford and Coggeshall (1981). Furthermore, it must be kept in mind that looping of primary afferent fibres into the ventral roots may occur (Coggeshall, 1980), resulting theoretically in the possibility that the same axon is counted three times. Finally, it would seem that the percentage of neurones that have axon collaterals in two somatic nerves is very low, judging by the electrophysiological studies of Devor et al.

(1984), who found only 14 of such neurones in 6400 neurones studied, including over 2700 neurones with unmyelinated axons. Similar negative electrophysiological results were obtained on neurones with unmyelinated fibres in rat hindlimb nerves by W. Jänig (unpublished observations), who recorded from axon bundles that had been sectioned distally: of 300–400 neurones, which projected in the sural or superficial peroneal or tibial nerve, no neurone could be activated by electrical stimulation of the other two nerves. In the trigeminal system, Borges and Moskowitz (1983) found only two doubly labelled cells out of 852 studied following application of different retrograde tracers to the intracranial and extracranial branches of the trigeminal nerve.

A major weakness of all the experimental evidence is that two functional receptive fields have never been found in neurones that show branching, and suggestions that they participate in referred pain must be tentative until functional information of this sort is available.

Properties of visceral afferents

Methods

The main body of experimental evidence on which the arguments in this review are based has been obtained in neurophysiological experiments on visceral spinal afferent neurones in cats; some experiments were also conducted on dogs, sheep and ferrets. In these experiments animals were anaesthetised, usually with alpha-chloralose or sodium pentobarbitone, and were often artificially ventilated and immobilised; various monitors of physiological conditions were used, so as to maintain the physiological state of the animal.

Afferent activity was recorded from single units dissected from visceral nerves, white rami, or sacral dorsal roots in a pool of paraffin oil, using standard techniques.

Mechanical and chemical stimuli were used to characterise the receptors: (1) Glass or nylon rods with fine tips, or cat's whiskers were used to determine the location and extent of the mechanosensitive receptive fields. (2) Passive distension of hollow organs with fluid (or air) at constant pressure, or by repeated injection of small volumes. (3) Isovolumetric or isotonic contraction of muscular viscera, either occurring naturally after filling, or elicited by nerve stimulation. (4) Tension applied to vessels and mesenteries, either manually or by means of a pulley system. (5) Vascular changes induced by injection of drugs, occlusion of the common carotid arteries, by occlusion of intra-abdominal arteries or veins, or by infusions into intra-abdominal veins. (6) Chemical stimuli applied intra-arterially, or by superfusion over the receptive fields of receptors; the chemicals included bradykinin, KCl, HCl and hypertonic saline. (7) Temperature changes could be applied by a thermode or superfusion of saline at different temperatures.

Receptive fields

The majority of mechanoreceptors in the spinal afferent pathway from viscera have receptive fields in a mesentery or peritoneal ligament and/or the adjacent viscus, and consist of between one and nine mechanosensitive spots distributed along the course of the nerves (periarterial nerves) innervating the viscera. Probing these endings, using forces often less than 10 mN, gives rise to a slowly adapting discharge. In compliant tissues with large surface area the receptive fields are sometimes larger than those described by Bessou and Perl (1966) and Morrison (1973). In the mesentery, the receptive endings occur particularly at sites where vessels divide, and are also common in the serosa, at the point where a vessel enters the wall of the viscus. Occasionally, mechanosensitive endings may be present within a solid viscus such as the liver, but they are usually confined to the mesenteric or peritoneal attachments. The endings can occur around veins, when these are not accompanied by arteries, such as along the portal vein as it passes through the pancreas.

Receptors with these properties have been found

throughout the abdomen, along vessels supplying all parts of the gastrointestinal and urogenital tracts, the lymph nodes, spleen, peritoneum and large vessels in cats, dogs and sheep (Bessou and Perl, 1966; Ranieri et al., 1973; Morrison, 1973, 1977, 1980; Floyd and Morrison, 1974; Cervero, 1982; Blumberg et al., 1983; Bahns et al., 1985a,b). About 120–350 Pacinian corpuscles are present in the mesenteries and pancreas of the cat; these sense organs have large myelinated fibres, and are extremely sensitive to vibrations transmitted from outside the animal.

Thermoreceptors and chemoreceptors have also been described in the spinal afferent pathway from viscera (Riedel, 1976; Hardcastle et al., 1978; Recordati et al., 1978, 1980, 1981; Perrin et al., 1981). Little is known of their receptive fields; their properties will be discussed later.

Adaptation

Bessou and Perl (1966) reported that most units adapted rapidly, but Ranieri et al. (1973), Morrison (1973, 1977), Floyd et al. (1976a), Blumberg et al. (1983) and Bahns et al. (1986a,b) found that local pressure usually produced slowly adapting responses. The probing of mechanosensitive sites with forces of 0.1 N or less produces responses which adapt with half-times of 2–8, 20–30 and 200–250 seconds (Morrison, 1977). During distension of viscera, the response of the units depends on the position of the ending with respect to the visceral movement, and adaptation can be rapid, lasting 2–3 seconds (Bessou and Perl, 1966), or slow (Morrison, 1973; Floyd et al., 1976a,b). Blumberg et al. (1983) found that 48% of colonic units adapted to a steady-state discharge, while most of the remainder adapted to the pre-existing resting discharge within 10–30 seconds; only 2% of the units responded by a very rapid, short-lasting burst of activity.

Conduction velocities

Apart from the mesenteric Pacinian corpuscles which have large-diameter axons, the remainder of the mechanoreceptors have fibres with Aδ- and C-fibre conduction velocities. Both groups of fibres are present in the thoraco-lumbar supply to all abdominal viscera (Ranieri et al., 1973; Morrison 1973, 1977; Floyd et al., 1976a; Blumberg et al., 1983; Bahns et al., 1986a,b). Nothing appears to be known about the properties of Aβ-fibres in renal nerves reported by Calaresu et al. (1978), but it seems likely that they originate from Pacinian or Paciniform corpuscles.

The conduction velocities of most sacral visceral afferent fibres which pass through the pelvic nerves and enter the spinal cord through the dorsal roots are also in the Aδ- and C-fibre range. The fastest conducting axons come from the urethra (range, 10–45 m/second; mean ± S.D., 25.2 ± 11.2 m/second, n = 12). Sacral afferents from the urinary bladder conduct at 12.7 ± 9.7 m/second (n = 31). No unmyelinated pelvic fibres responding to distension and contraction of the urinary bladder have been found. Afferents from the anal canal conduct at 9.8 ± 5 m/second (n = 35) and sacral afferents from the colon are the slowest conducting, some of them being unmyelinated (4.8 ± 5 m/second, n = 12) (Bahns et al., 1985a).

Most sacral ventral root afferents supplying pelvic organs are unmyelinated (Applebaum et al., 1976; Clifton et al., 1976; Coggeshall and Ito, 1977). Whether or not these fibres are collaterals of visceral neurones which also have a branch in the dorsal roots, is unclear (for further discussion, see p. 92).

Ongoing activity

Thoraco-lumbar visceral afferents

Many papers report that mesenteric Pacinian corpuscles in the cat commonly show cardiovascular rhythms, as might be expected of receptors that are specialised to pick up low-amplitude, high-frequency vibrations (Talaat, 1937; Gernandt and Zotterman, 1946; Winter, 1971; Ranieri et al., 1973). The Aδ- and C-fibre mechanoreceptors in the thoraco-lumbar afferent pathway from the bladder, colon, small intestine, kidney, renal pelvis,

liver, billiary tract, the thermoreceptors in the dorsal abdominal wall, and one group of renal chemoreceptors also show ongoing activity. In some units the discharges are not related to any obvious mechanical event of the viscera, while others are modulated by arterial, respiratory or gastrointestinal movements (Talaat, 1937; Bessou and Perl, 1966; Andrews and Palmer, 1967; Beacham and Kunze, 1969; Winter, 1971; Ranieri et al., 1973; Riedel, 1976; Recordati et al., 1980; Cervero, 1982; Blumberg et al., 1983; Bahns et al., 1986a,b). The rhythms probably indicate that sensitive receptors are located near arteries, veins or visceral muscle. In some instances it is possible to modify the rhythm by moving the tissue in which the sensory endings are present. Other rhythms are probably not explained by local movements, e.g., the activity in pre-renal and retroperitoneal receptors (Ranieri et al., 1973; Bahns et al., 1986b).

The rates of ongoing activity vary from 1 spike every 2–10 seconds (Coggeshall and Ito, 1977; Blumberg et al., 1983; Bahns et al., 1986a,b) to 10–25 impulses per second (Ranieri et al., 1973). More than 50% of units exhibit ongoing activity (Bessou and Perl, 1966; Ranieri et al., 1973; Blumberg et al., 1983; Bahns et al., 1986a,b).

It may be argued that the ongoing activity in thoraco-lumbar visceral afferents does not normally occur in physiological (non-painful) conditions, and that it is due to the experimental, surgical and stimulation procedures used. Though the latter cannot be denied completely, there is, at least from some studies, ample evidence showing that the ongoing activity — in its rhythm as well as in its spike rate — also occurs with the visceral organs being in situ in their natural environment, with the peritoneum intact (Floyd et al., 1976b; Morrison, 1977; Blumberg et al., 1983; Bahns et al., 1986a,b).

Sacral visceral afferents

In contrast, there are few reports of ongoing activity in the pelvic nerve afferents. Talaat (1937), Iggo (1955) and Floyd and Lawrenson (1979) did not report any activity. Bahns et al. (1985a,b) did not find any afferent units with ongoing activity from the urinary bladder and urethra, but occasionally observed some from the anus.

Responses to distension and contraction

Mechanical considerations

The response of afferent neurones to distension of viscera has to be considered in relation to the normal capacity and function of the organs. The pressure-volume curves of most viscera show that they are compliant within the physiological range, but that small increases in volume within the supraphysiological range cause pressure to rise sharply. To some extent the gradient of this part of the curve and the volume at which the gradient increases are dependent on the tone of smooth muscle and the actions of its motor nerve supply (Gjone, 1966; Edvardsen, 1968). In addition, the rate of inflation can influence the gradient of the filling phase of the pressure-volume curve, and in normal situations the bladder accomodates to increased volume with little change in intravesical pressure (Klevmark, 1974, 1977). In man, the speed of fast cystometry prevents accomodation from occurring and there is a significant rise in pressure at physiological levels of distension, and the maximum volume subjects can tolerate in these conditions is less than the volume they would normally void (Abrams and Torrens, 1979). Finally, low levels of distension can induce changes in motility in most viscera; sensation is commonly associated with these reflex contractions (Schuster, 1968; Turner-Warwick, 1979), and the size of the contractions and intensity of the sensation increase if the movement of the visceral contents is resisted by some obstruction. Thus, the change from isotonic to isovolumetric recording conditions abolishes flow and increases the pressure developed in the closed system (Mellanby and Pratt, 1940) and the responses of visceral afferents that respond to contractions (Iggo, 1955, 1966). In some viscera the occurrence of contractions can be irregular in time and force, and may be localised, propagated, or involve the whole organ. In isovol-

umetric conditions, contractions are inevitably accompanied by stretch of in series elastic elements in the viscus, such as elastic tissue or inactive smooth muscle. Thus, during isovolumetric conditions, bladder contractions cause distension of the proximal urethra, and endings opposed to this part of the viscus can be excited by displacement of fluid from the bladder. This local change may be minimal in isotonic conditions, in which there are large changes in the volume of the bladder itself (see Lapides, 1958). Distension of the proximal urethra may be associated with a sensation that micturition is imminent, which is sometimes referred to as urgency.

Urinary bladder and urethra

Distension of the bladder can excite receptors in the pelvic (PN) and hypogastric (HGN) nerves. The urethra is innervated in addition by the pudendal nerve (Todd, 1964; Downie et al., 1984) and the main electrophysiological studies on urethral afferents are by Bahns et al. (1985a,b, 1986a) and Todd (1964).

Pelvic nerve

Fig. 6 shows that several workers have found the range of pressure thresholds in afferents from the bladder to be within the physiological range; attempts to find units with high thresholds have been unsuccessful (Floyd and Lawrenson, 1979, and unpublished data; Bahns et al., 1985a). G. Lawrenson (unpublished data) found that the pressure thresholds all fell on the flat compliant part of the pressure-volume curve, at about 25–75% of the pressure at which the curve became steep. These thresholds are quite consistent with the conditions under which humans report the first sensation of filling during cystometry (Torrens and Abrams, 1979). The stimulus-response relationships during distensions have been examined in conditions which abolish reflex bladder contractions, either by adding 5–20 ml of saline to the viscus every 3–5 minutes (Floyd and Lawrenson, 1979) or by increasing the head of pressure applied to the organ from zero to a constant level for 90 seconds (Bahns et al., 1985a; see also Bahns et al., 1986a). In the former conditions, the relationship between discharge rate and intravesical pressure becomes less steep or plateaus at pressures that correspond to the steep part of the pressure-volume curve. In the latter experiments, spike rate increased almost linearly with rise in pressure. The difference can probably be attributed to adaptation in Floyd and Lawrenson's experiments, as it could take 20 or more minutes to reach high intravesical pressures using that protocol. Slow filling is more physiological than rapid distension (Klevmark, 1974, 1977). Winter (1971) attempted to record from bladder afferents during slow filling. His recordings were from a mixed population of PN and HGN units and were dominated by excitation due to reflex contractions, which occur at low volumes in anaesthetised, but not in awake cats (Klevmark, 1980).

PN afferents can also register the size and timing of bladder contractions (Evans, 1936; Talaat, 1937; Iggo, 1955, 1966; Arlhac, 1971; Winter, 1971; Floyd and Lawrenson, 1979; Bahns et al., 1985b). Iggo (1966) reported that the responses during contractions could be variable, due to the relative positions of receptive endings and contracting muscle, and that the responses were larger in isovolumetric than in isotonic conditions. By changing from isotonic to isovolumetric recording conditions during a contraction, Mellanby and Pratt (1940) observed a marked increase in intravesical pressure, which was accompanied, in Iggo's experiments (1955, 1966), by a marked increase in the rate of discharge of PN afferents. In humans, these conditions are simulated during rapid voluntary interruption of micturition; Turner-Warwick (1979) reports that under these conditions a sensation of desire to void occurs as soon as urine flow stops and lasts until the smooth muscle of the bladder relaxes.

The thresholds of PN afferents during bladder contractions have been studied by Bahns et al. (1985b), using irregular contractions that occurred either spontaneously or were evoked. The thresholds were within the range 5–15 mmHg (see Fig. 6). These thresholds are within the physiological range

for contractions: during micturition in normal humans the bladder pressure reaches 30–40 mmHg. Morrison (1981) reported that sympathetic stimulation could reduce the responses of PN afferents and of spontaneous bladder contractions in the cat. It is clear that PN afferents provide the cord with accurate information concerning the size and timing of bladder contractions.

All of the PN recordings mentioned above were from myelinated fibres, and the only reports of unmyelinated bladder afferents that enter the sacral cord were from Applebaum et al. (1976) and Coggeshall and Ito (1977) in sacral ventral roots. However, it must be kept in mind that they determined the conduction velocities between two pairs of recording electrodes which were positioned about 4–8 mm apart at the ventral root filaments. Thus, it might well be that some of their unmyelinated units were branches of myelinated fibres. The majority of their units responded to distensions, but not to contractions; however, a few responded to both. The receptive fields of these units were not investigated and may have been extravesical; also, no information on stimulus-response relations is available for these units.

Hypogastric nerve

Recent work on HGN afferents from the bladder suggests that they behave similarly to those in the PN (Floyd et al., 1976a; Morrison, 1981; Bahns et al., 1986). In these studies, 50% of afferent units had thresholds of 8–15 mmHg (see Fig. 6). Earlier studies by Talaat (1937) suggested the presence of high-threshold afferents, but these recordings were complicated by previous denervation of the PN supply to the bladder, and by the lack of unitary recordings: Talaat's conclusions about HGN afferents were based on studies of "slow waves" that he observed at high volumes. The stimulus-response relationship during contractions is linear (Floyd et al., 1976a; Bahns et al., 1986a); contractions have been studied either by stimulating the sacral cord after a transection at L6, so as to obtain an adapted discharge rate at a constant intravesical pressure, or by observing responses to irregular contractions, produced during recovery from spinal anaesthesia. No functional differences were observed between the Aδ- and C-fibre populations in the HGN, except that the spike rates in the latter group were lower.

Colon and anus

Pelvic nerve

Little information is available about the sacral afferent pathway from the colon, and most of that derives from studies of ventral root afferents. Threshold pressures of 11 mmHg upwards have been reported, and some units were insensitive to distension (Clifton et al., 1976; Coggeshall and Ito, 1977; Floyd et al., 1976c; Morrison and McMahon, 1982). U. Halsband and W. Jänig (unpublished data) have recently found that colonic afferents in S1 and S2 dorsal roots usually have thresholds of 20–40 mmHg.

The mucosal skin of the anus is supplied by sacral afferent fibres that pass through the pelvic nerves and dorsal roots. These afferents have unique functional properties, probably indicating their special role in eliciting reflexes and sensations. They respond vigorously to mechanical shearing stimuli of the mucosal skin and less vigorously or not at all to distension and noxious stimuli (Bahns et al., 1985a). This class of spinal visceral afferents appears to be quite distinct from most other types of spinal visceral afferents; exciting them by shearing stimuli elicits most powerful spinal reflexes in lumbar preganglionic "motility-regulating" neurones (Bahr et al., 1986; Bartel et al., 1986).

Hypogastric and lumbar splanchnic nerves

Blumberg et al. (1983) have reported that lumbar splanchnic afferents from the colon usually have thresholds of around 25 mmHg, and the histogram of thresholds tailed off at high pressures, where a few units responded to 50–75 mmHg. Most units showed ongoing activity, and excitation during distension. The units that did not respond probably were postganglionic efferents (they could not be activated by any mechnical or chemical stimulus

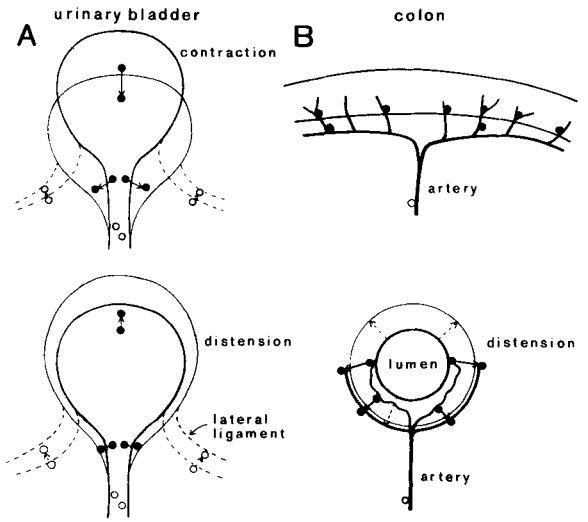

Fig. 5. Change of position of visceral receptors during contraction and distension of visceral organs. Positions of receptors which are excited by these procedures are indicated by dots. Positions of receptors which are not excited or only weakly excited with a few spikes at the beginning of a distension or a contraction are indicated by circles.

(Blumberg et al., 1983; Haupt et al., 1983)) or did not respond because of the position of their receptive field in relation to the distended portion of colon. Many of these units were in the mesentery rather than on the colonic wall. For less than half of the units only, which responded to distension, the receptive fields were localized because of the inaccessibility of one side of the colon. These positional factors may be responsible for the variation between units in their rates of adaptation: four classes were identified according to their behaviour during distensions lasting 60 seconds. Positional factors may also be responsible for the low slope of some of the stimulus-response curves from this organ shown in Fig. 6. Fig. 5B indicates some of the mechanical changes that occur during distension of the colon that affect the transmission of forces to receptive endings.

The studies of Floyd et al. (1976a), Morrison (1977, 1982) and Blumberg et al. (1983) suggest that the thresholds of these units during contractions are low, and that the units respond to spontaneous peristaltic contractions; no stimulus-response curves are available however.

Biliary tract

Reports on the effects of distension of the biliary tract on spinal afferents have been made by Morrison (1981) in the cat and Cervero (1982, 1983) in

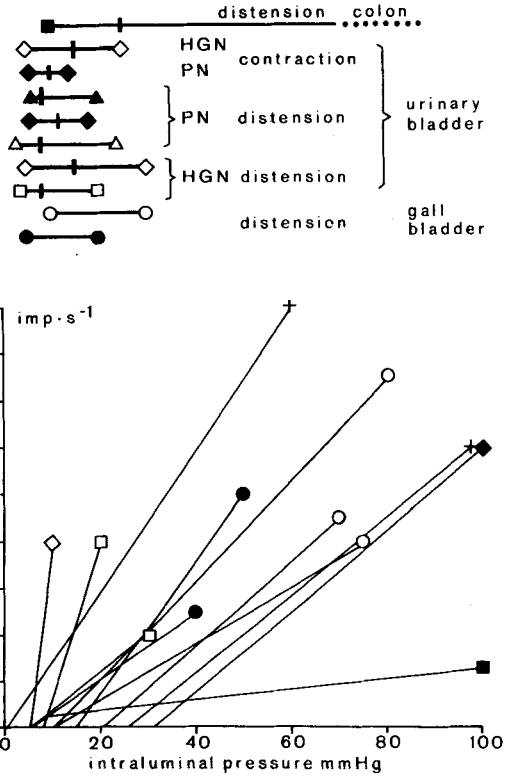

Fig. 6. Thresholds and stimulus-response relations of thoracolumbar and pelvic visceral afferents to contraction and distension of colon, urinary bladder and gallbladder. Upper part: range of thresholds of primary afferents to distension and contraction. The medians are indicated by the vertical bars. HGN, hypogastric nerve; PN, pelvic nerve. Data from: colon (■), Blumberg et al. (1983); HGN (□), Floyd et al. (1976a), (◇), Bahns et al. (1986a); PN (◆), Bahns et al. (1985b), (▲), Talaat (1937), (△), Morrison (1981); gallbladder (○), Cervero (1983), (●), Morrison (1980). Lower part: representative simplified stimulus-response relations of visceral afferent units from urinary bladder, colon and gallbladder to distension. +, pelvic nerve units to colon distension (Morrison, 1982), otherwise symbols as above.

the ferret. The published data indicated thresholds in the range 5–20 mmHg and stimulus-response curves that were not dissimilar to those from other viscera (see Fig. 6). Units along the portal vein and bile duct did not always respond to a rise in biliary pressure, probably because of their position. Cervero divided his units into low- and high-threshold groups depending on the relationship of the activity of his units to opening of the sphincter of Oddi or to a rise in arterial pressure. Little information was provided about the absolute pressures necessary for activation, and the data used in Fig. 6 are taken from one of Cervero's figures. We can see no clear reason for attempting to divide these units into separate groups as they represent, in our view, different parts of the spectrum of properties shown by afferents from most viscera. These variable properties can be attributed to differences in compliance of the tissues, and to differences in the position of receptive endings. In Morrison's (1981) report, some endings that responded to an increase in venous pressure also gave meagre responses at high biliary tract pressures, and this is again probably due to the position of the endings rather than to basic differences in transducer function.

Stomach and small intestine

It is clear that some afferent units in these viscera have thresholds as low as 5–8 mmHg, although many small intestinal units need at least 25 mmHg, to be excited; they have not been studied as systematically as those innervating the bladder and colon. Ranieri et al. (1973) found that afferents from the stomach discharge during the rising phase of, or throughout, gastric contractions. Units in the lesser omentum and diaphragmatic surface can also be activated by gastric movements, either because of spread of forces into local structures or because of friction between peritoneal surfaces. In the small intestine, peristaltic movements also excite spinal afferents (Gernandt and Zotterman, 1946; Bessou and Perl, 1966; Ranieri et al., 1973).

Ureter and renal pelvis

At the upper end of the ureter and at the renal hilum there is a dense plexus of nerves (Gosling, 1969, 1970; Dixon and Gosling, 1971). Beacham and Kunze (1969) found sensitive mechanoreceptors that responded to increased venous pressure or ureteric pressure at this site. The thresholds for venous pressure could be as low as a few mmHg, but were usually greater than 15 mmHg for ureteric pressure. At the lower end of the ureter sensitive mechanoreceptors can respond phasically to increases in bladder pressure (Floyd et al., 1976a) and sometimes to the passage of a peristaltic wave along the ureter (E. Bahns and W. Jänig, unpublished observations).

Tension on mesenteries; vascular factors

Most workers agree that the application of forces that distort the mesentery and its perivascular endings causes a discharge whose intensity is related to the force applied (Bessou and Perl, 1966; Ranieri et al., 1973; Morrison, 1973, 1977; Blumberg et al., 1983; Bahns et al., 1986a). Forces of a few tens of mN are necessary to activate the endings, and the stimulus-response curves are approximately linear; Floyd and Lawrenson (1979) reported thresholds of 0.007–0.4 N/mm in the bladder and colon. It is not surprising that sensitive receptors within a compliant structure, such as the mesentery, respond to local forces produced by biological events, such as repiratory movement (Andrews and Palmer, 1967; Morrison, 1973; Ranieri et al., 1973; Cervero, 1982), arterial pulsation (Bessou and Perl, 1966; Morrison, 1973, 1977; Ranieri et al., 1973; Bahns et al., 1986b), venous distension (Andrews and Palmer, 1967; Beacham and Kunze, 1969; Morrison, 1973, 1980) or gastrointestinal movement (Bessou and Perl, 1966; Morrison, 1973; Ranieri et al., 1973; Blumberg et al., 1983), depending on the position of the ending. They often show ongoing activity

that is modulated by these events (see above). Some also respond to sliding of one peritoneal surface over another.

Sensitivity to chemicals

Injection of bradykinin (BK), one of the most potent algogenic substances known to man, into the peritoneal cavity or the splenic artery produces pseudoaffective reflexes and antinociceptive actions in animals (Lim, 1960, 1970; Lim et al., 1962, 1964, 1967; Le Bars et al., 1979). The peptide is known to excite fine myelinated or unmyelinated afferents that may be involved in nociceptive functions from skin, muscle and viscera (Beck and Handwerker, 1974; Uchida and Murao, 1974; Franz and Mense, 1975; Handwerker, 1976; Floyd et al., 1977; Kumazawa and Mizumura, 1977, 1980; Mense, 1977, 1985; Nishi et al., 1977; Baker et al., 1980; Lombardi et al., 1981; Haupt et al., 1983; Bahns et al., 1986b) and also afferent fibres that are probably not involved in nociception (Fjällbrandt and Iggo, 1961; Beck and Handwerker, 1974).

Floyd et al. (1977), Haupt et al. (1983) and Bahns et al. (1986b) found that mechanoreceptive afferent units from the bladder, colon, uterus, pancreas, spleen, small intestinal mesentery and peritoneal lining of the posterior abdominal wall were usually excited by BK, administered intra-arterially or by superfusion of the receptor site. No Aδ- or C-fibre afferents were found that showed chemosensitivity without mechanosensitivity, but this view is not held by Longhurst et al. (1984), who maintain that visceral afferent C-fibres in the thoracic white rami that responds to BK are not mechanosensitive. Their A-fibre population must have included Pacinian corpuscles as the range of conduction velocities was up to 84 m/second.

It seems likely that BK can have some direct action on at least some visceral nerve endings, because superfusion of mesenteric receptors with the drug causes excitation. However, muscular contraction probably plays a part in most situations, and in some viscera, such as the bladder, the responses to BK are reduced or abolished if contractions are prevented from occurring (Floyd et al., 1977). Paralysis of the colon, however, does not abolish the response to BK (Haupt et al., 1983).

Other intraperitoneal chemical stimuli, such as KCl, HCl, acetic acid and hypertonic saline, elicit pupillary dilatation in chloralosed cats and writhing in rats (Downman et al., 1948; Giesler and Liebeskind, 1976; Le Bars et al., 1979). Haupt et al. (1983) found that lumbar colonic afferents responded to intra-arterial KCl by producing short-lasting, high-frequency bursts, particularly if the units exhibited ongoing activity in the absence of external stimuli, whereas hypertonic saline (injected intra-arterially) had little effect. The effects on the units were highly correlated with their responses to colonic distension and BK. Schmitt (1973) reported that the portal injection of hypertonic solutions modulated the discharge of hypothalamic neurones in rats, and depended on a splanchnic afferent pathway. More than 90% of lumbar afferent units from vessels, nerves, lymph nodes, fat and parietal peritoneum responded to local application of hypertonic NaCl solution (4.5 or 9%) and about 75% responded to local KCl (60 and 155 mmol/l) (Bahns et al., 1985b).

Beacham and Kunze (1969) recorded from renal nerve afferents in the cat and found that they responded to small elevations of renal venous pressure (1–2 mmHg) and to increasing ureteral pressure by more than 15 mmHg. These units, like the renal "baroreceptors" described by Niijima (1971, 1972, 1975), also responded to probing the renal hilum, and appeared to be mechanoreceptors: the relationship between these units and the renal chemoreceptors in the rat is unclear (Recordati et al., 1978, 1980, 1981). One group of renal chemoreceptors (Recordati et al., 1980) are excited by backflow of non-diuretic urine into the renal pelvis, apparently because of a change in the chemical composition of the renal interstitium produced by ions crossing the papillary epithelium, leakage from ischaemic cells, or alterations in renal blood flow or excretion of fluid and electrolytes. These units show ongoing activity in the non-diuretic state and re-

spond to elevation of ureteral pressure, apparently by modifying the chemical environment around the nerve endings. However, Recordati et al. (1980) appear not to have tested directly for mechanosensitivity, and it is unclear whether they accept the existence of a separate population of renal mechanoreceptors or whether they believe that all units that respond to raised ureteric pressure are specific chemoreceptors.

Temperature and ischaemia

Heating the wall of the small intestine to over 46°C dilates the pupil of the chloralosed cat and elicits an intestino-intestinal inhibitory reflex (Chang and Hsu, 1942; Downman et al., 1948). The sensitivity of spinal visceral afferents to thermal stimuli has not been studied in detail, but mechanosensitive units in the retroperitoneal space which respond to local application of BK, KCl and hypertonic saline may also respond to heat stimuli of more than 42–44°C (Bahns et al., 1986b). Thus, responses to intra-abdominal heating need not depend on a specific group of afferent units excited by heat.

Intra-abdominal heating to 42–44°C using a thermode causes thermoregulatory changes in sheep, and these can be abolished by splanchnic nerve section (Rawson and Quick, 1970, 1972). The role of these receptors in sensation is unknown, but observations in rabbits have suggested the existence of specific thermoreceptors with unmyelinated fibres in the dorsal abdominal wall. These units were unaffected by mechanical stimuli, and two populations, with static and dynamic maxima at 40 and 46°C, respectively, were identified (Riedel, 1976).

The effects of ischaemia on spinal afferents have been studied in the colon and in the kidney. Haupt et al. (1983) found that colonic units that responded to distension and to BK were also excited by ischaemia; a bursting pattern of discharge was induced, and potentiation of the reponse to colonic distension was observed, along with an increase in cardiovascular reflex effects of distension and BK. Recordati et al. (1980) found renal receptors that were insensitive to changes in arterial, venous or ureteral pressure, but were excited by renal ischaemia. These endings produced bursts of impulses during occlusion of the renal artery, severe hypotension or prolonged renal venous stasis.

Sensations and visceral afferent activity

Types of pain and other sensations elicited from viscera

Some perceived visceral sensations provide relatively precise information upon which the brain can act and initiate an appropriate behaviour. The information relayed by a relatively small number of afferents from the lower urogenital and gastrointestinal tracts confers the ability to distinguish not only between fullness of different viscera, e.g., the bladder or rectum, or between the presence of flatus or faeces in the latter, or between different stages of sexual activity, but also to assess to some extent the degree of filling of one of the reservoir organs. The site, intensity, timing and nature of these normal visceral stimuli can be perceived. Certain stimuli, such as heat, do not elicit sensation, when applied to the bladder (Nathan, 1952b). In contrast, during overdistension, discomfort or overt pain occur, and differ in that they are vague and diffusely localized (usually), and the source of the pain commonly has to be deduced from observations of how the pain changes with different motor acts, such as defaecation or micturition. On the first occurrence of a visceral pain, the patient has no framework of reference to decide on its origin: the site of the pain often bears no relation to the site of the organ from which it originates. The pain is described as abdominal rather than visceral, and the patient has usually to rely on a trained observer to discern the source of the pain; that diagnosis depends, at least partly, on an understanding of the peripheral organisation of spinal visceral afferent pathways. Therefore, visceral pain is a diagnosis rather than a symptom.

The relationship between the location of true visceral sensation and segmental innervation

Figs. 3 and 4 summarise the available information on the size and segmental distribution of the afferent innervation of different viscera in the cat and rat. The density of the spinal innervation of each viscus is maximal in one or two adjacent segments, and there are a few segments of the lower lumbar cord that do not participate in visceral innervation; the somatic structures innervated by these segments, i.e., structures below the knee, are usually not involved in referred pain. In the cat, the peak density of neurones innervating the kidney, colon and bladder occurs in the second, third and fourth lumbar segments, respectively; the colon and bladder are also innervated by sacral afferent neurones that are most numerous in the second sacral segment. In man, the sacral innervation is more caudal, whereas in the rat it is more rostral and extends into the lumbar cord. The afferent innervation of viscera may be entirely unilateral, as in the kidney, predominantly unilateral, as in the liver, or bilateral, as in the colon.

The site of true visceral pain (see Lewis, 1942) appears to be determined by the segmental origin of the afferent innervation of the viscus and its degree of lateralisation; the higher the segmental origin of the afferent fibres, the more rostral the abdominal pain. The importance of these factors was emphasised by White (1943) and White and Sweet (1969). These neurosurgeons transected white rami at different segmental levels to treat pain of visceral origin, and were able to map the distribution of "pain pathways" from the viscera. Fig. 7 summarises the denervations that were necessary to relieve pain originating from different viscera. The major afferent pathways that subserve pain from a viscus enter the cord in a relatively small group of segments, the distribution of which is remarkably similar to those that are principally concerned with the afferent innervation of the viscus in the cat or rat (Figs. 3 and 4), given minor rostro-caudal adjustments in the different species. In the case of the colon, the lumbar denervations were insufficient to relieve pain, probably due to the integrity of the sacral innervation of this viscus. Ruch (1979) describes a "pelvic pain line" which delineates viscera, in which pain sensation depends on a sacral afferent pathway. This concept, based largely on the work of White (1943), is quite consistent with modern neurosurgical experience; Torrens and Hald (1979) report that a selective neurectomy in the third sacral segment in man abolished painful frequency and urgency in patients whose lower urinary tract physiology had been well investigated. Pain arising from viscera that receive an afferent supply from lumbar and sacral segments may be located both suprapubically (upper lumbar innervation) and in the perineum (sacral innervation). Distension of balloons in the upper, middle and lower thirds of the gastrointestinal tract gives rise to pain above, around or below the umbilicus (Lipkin and Sleisenger, 1958). These pains are usually felt in the midline, either in the front or, less commonly, in the back of the abdomen. However, if the innervation of the viscus is entirely from one side of the cord, the sensation is ipsilateral; viscera that are innervated mainly from one side tend also to give rise to pain on the side of the body that has the greatest innervation. Evidence that the degree of lateralisation of the innervation determines the side of the abdomen in which pain is perceived comes from experiments on humans who have the afferent pathway from the viscera sectioned surgically on one

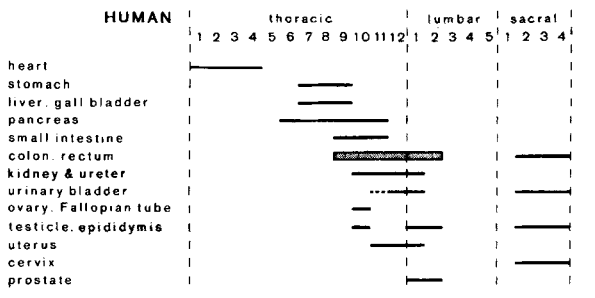

Fig. 7. Relief of visceral pain by transection of white rami and sacral dorsal roots. Section of the number of white rami and sacral dorsal roots indicated by the length of the black horizontal lines. The stippled area indicates the lesions which did not relieve colonic pain, presumably due to the integrity of the sacral innervation. From White (1943) and White and Sweet (1969).

side of the body: in these patients, distension of the jejunum gives rise to pain, not in the midline as would occur in normal individuals, but on the side of the body that still receives afferent information from the viscus (Bentley and Smithwick, 1940). In normal individuals some viscera are innervated mainly from one side of the spinal cord, and the distribution of visceral pain is lateralised. Thus, kidney pain is invariably lateralised to the loin or flank, and biliary tract pain is commonly lateralised to the right upper quadrant (Gaensler, 1951; Risholm, 1954). (Two-thirds of the spinal innervation of the liver and biliary tract in the rat is from the right side of the cord.) Pain referred from the biliary tract to the right shoulder tip can also be explained by the innervation of the biliary tract from the right phrenic nerve (Hazarika et al., 1964). Thus, the site of abdominal pain that arises from a viscus depends partly on the level of the spinal segments that innervate the viscus, and the degree of lateralisation of that nerve supply.

The involvement of sacral as well as thoracolumbar spinal segments in visceral pain mechanisms can also be deduced from studies of the distribution of cutaneous hyperalgesia, deep tenderness and referred pain in visceral disease (see McKenzie, 1909; Lewis, 1942). Fig. 8 shows the distribution of cutaneous hyperalgesia (Head, 1893), deep tenderness (Hansen, 1963) and the distribution of referred pain

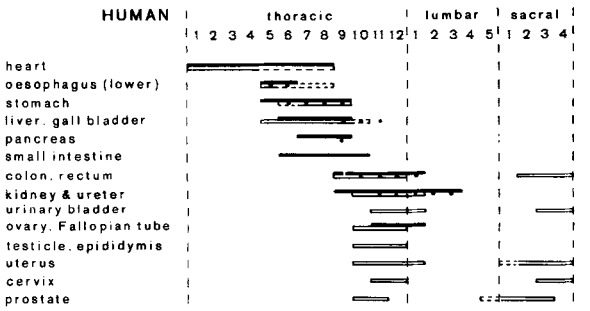

Fig. 8. Segmental distribution of cutaneous and subcutaneous hyperalgesia occurring spontaneously or elicited by pressure, and of tenderness during affection of visceral organs. Solid bars, Hansen (1963); open bars, Head (1893); dots, relief of referred pain by paravertebral blocks (from Flowers and Kappis, in Hansen, 1963; Läwen, 1922, 1923).

that could be abolished by cutting different spinal roots (see Flowers and Kappis, in Hansen, 1963). The similarity of these distributions with those known to mediate true visceral pain (Fig. 7) is remarkable.

The relation between sensation, reflexes and afferent activity: adequate stimuli

Fig. 9 summarises the available information on the levels of distending pressures that evoke innocuous and noxious sensations in man, and reflex activity in spinal afferent neurones in animals, principally cats. There can be considerable variation in different reports, which seems to depend on the methodology employed; e.g., the thresholds depend on the time for which distension is applied (Lipkin and Sleisenger, 1958), the length of the distended segment (of bowel) (Peterson and Youmans, 1945) and the occurrence of reflex contractions (Payne and Poulton, 1923; Denny-Brown and Robertson, 1933: Schuster, 1968). This figure demonstrates the differences in regional sensitivity to visceral distension that were demonstrated by Irving et al. (1937) in the chloralosed cat, and by other workers who studied sensory thresholds in man. Sensitivity to distension decreases in the following order: pylorus, biliary tract, upper ureter, oesophagus, colon, small intestine and terminal ileum. The extent to which these regional differences in sensitivity depend upon the density of innervation of the organs is unknown. The terminal ileum and middle ureter are apparently insensitive to pressures of 100–200 mmHg (Irving et al., 1937; Risholm, 1954). The position of the urethra in this sequence is unclear: the urethral sphincter normally exerts a pressure of 80–100 cm H_2O, and distension of the proximal urethra with 100 cm H_2O in Denny-Brown and Robertson's (1933) experiments did not elicit sensation. As a general rule, the reflex thresholds are less than the noxious sensory thresholds, and can be as low as the innocuous sensory threshold in viscera such as the bladder and colon. The latter is not surprising since numerous investigators have noted

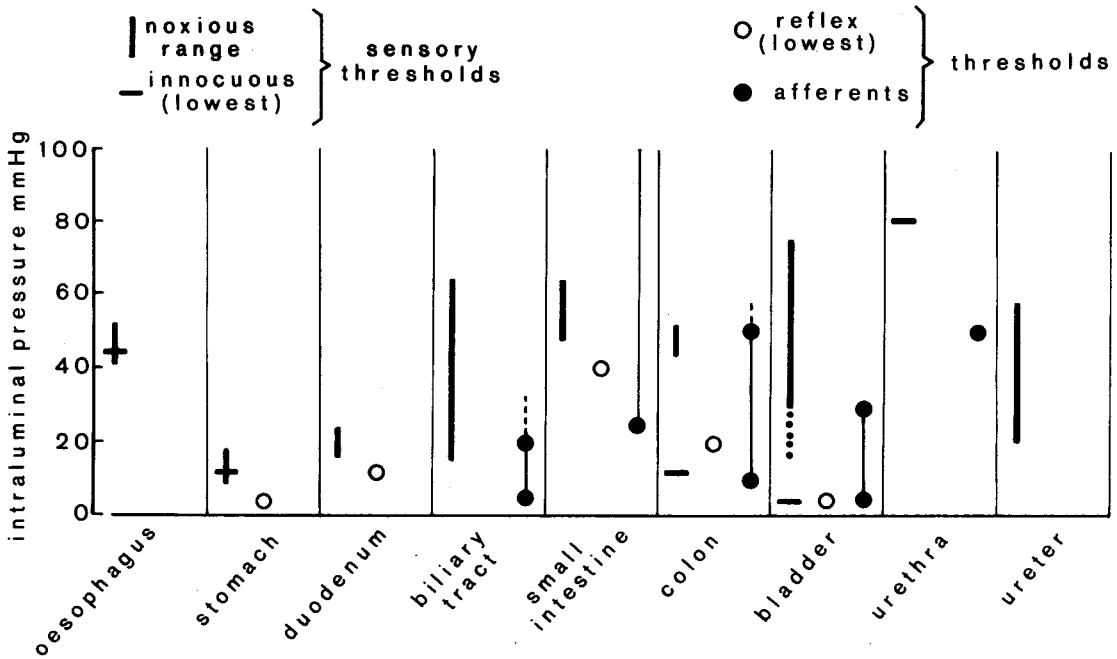

Fig. 9. Summary of data on intraluminal pressures that elicit innocuous and noxious sensations in humans, pupillary and visceral reflexes, and excitation of spinal afferents from viscera. Data on innocuous and noxious sensations in humans from: Payne and Poulton (1923), Denny-Brown and Robertson (1933, 1935), Gaensler (1951), Nathan (1952a, 1956), Risholm (1954), Lipkin and Sleisenger (1958), Murphy and Schoenberg (1960), Scott et al. (1964), Code and Carlson (1968), Cohen and Wolff (1968), Hightower (1968), Schuster (1968). Data on pupillary and visceral reflexes from: Irving et al. (1937), Ravdin et al. (1942), Youmans (1944), Peterson and Youmans (1945), Abrahamsson (1973), Floyd et al. (1982), McMahon and Morrison (1982), McMahon et al. (1982). Data on excitation of spinal afferents from viscera from: Floyd et al. (1976), Morrison (1980, 1981, 1982), Cervero (1982, 1983), Blumberg et al. (1983), Bahns et al. (1986a), Bahns, unpublished observation.

the occurrence of sensation in association with contractions (see later). The thresholds of the afferent units in cats, and the "specific nociceptors" from the biliary tract in ferrets (Cervero, 1982) were usually below the range of noxious thresholds reported in man. These interpretations depend on the assumption that no species differences occur between cats and humans with respect to these thresholds: the parallel nature of the regional variations in cats and humans suggests that they may be similar. In the absence of good behavioural data on animals, the choice is between this correlation: observations on cardiovascular reflexes in animals (see Cervero, 1982) or measurements of the visceral pressure that is necessary to induce DNIC-like (diffuse noxious inhibitory control) activity (see Lumb, this volume).

Most visceral receptors are directly or indirectly associated with smooth muscles of the gastrointestinal and urogenital tracts and vascular system: contraction of smooth muscle can modulate the excitability or may lead to excitation of visceral receptors, by changing visceral compliance or by altering the spatial arrangement of receptive structures and smooth muscles (see Fig. 3). These muscles are controlled by extrinsic sympathetic and/or parasympathetic nerves, and — as far as the gastrointestinal tract is concerned — by the activity of neurones in the enteric nervous system. Thus, the excitability of many visceral receptors not only depends on the adequate stimuli acting in the periphery and on the "tone" and activity of smooth muscle, but also on extrinsic and intrinsic neuronal ac-

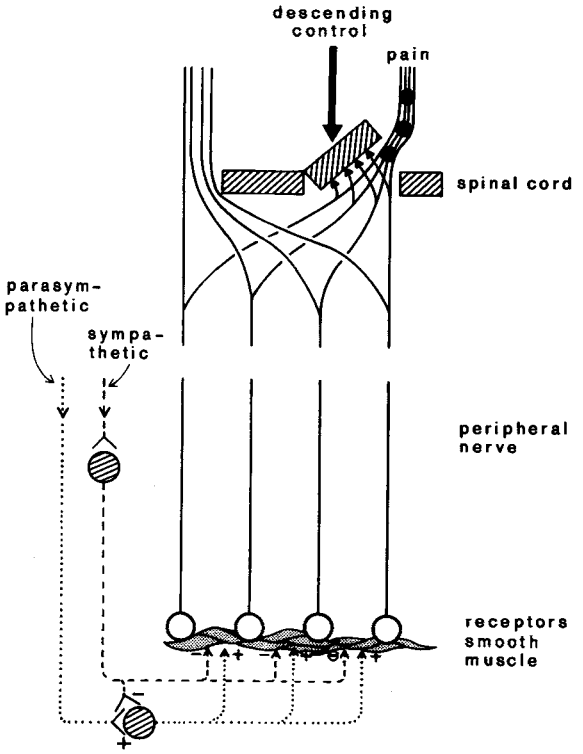

Fig. 10. Functional scheme on the interposition of most spinal visceral afferent neurones between peripheral visceral tissues and the second-order neurones in the spinal cord. At the level of the receptors, the excitation of the afferent neurones depends not only on the adequate physical and chemical stimuli but also indirectly on the activity of the extrinsic and intrinsic autonomic nervous systems and on the state of the smooth muscles (viscero-elastic properties, myogenic activity). The central decoding process of spinal visceral afferent information, for inducing sensations and reflexes, is indicated by a hypothetical gating mechanism. This mechanism must not be restricted to the spinal cord and may consist of multiple gates. For details see text.

tivity (see Fig. 10) (Iggo, 1955, 1966; Morrison, 1977, 1981; Blumberg et al., 1983; Bahns et al., 1986b). The role of the inhibitory efferent supply to the viscera in suppressing sensations of desire to void (McDowall, 1960), for example, is not known, but it cannot be assumed that the sites of interactions which exert some control over visceral sensation occur only within the central nervous system. Furthermore, since activities such as micturition and defaecation are separated by hours or days, it would need receptors that show extremely slow adaptation to monitor the fullness of viscera on a continuous basis; it is possible that voluntary or involuntary contractions play a part in bringing receptors into action in such a way as to allow the degree of distension to be sensed, possibly by comparing afferent activity with the efferent command signal, in a manner similar to that proposed for proprioception (McCloskey, 1981). Thus, contractions need not be regarded simply as reflex events, and could play a part in eliciting visceral sensation.

The top of the range of pressures exerted during spontaneous contractions of viscera may exceed the bottom of the range of noxious sensory thresholds, e.g., in the colon. These contractions are of short duration, and the thresholds given are the minimum pressures that can elicit pain after a period in excess of 20 seconds (Lipkin and Sleisenger, 1958). Contractions accompanied by movement of visceral contents or voiding may not sustain an adequate level of receptor excitation for a long enough period to elicit sensation, but there is little doubt that contractions of viscera themselves evoke sensations that may be uncomfortable, e.g., colic (Payne and Poulton, 1923; Connel et al., 1965; Schuster, 1968). During normal micturition, the isotonic contraction causes intravesical pressure to rise to around 30 mmHg (Murphy and Schoenberg, 1960; Shah, 1984). Voluntary interruption of voiding when the bladder is half full gives rise to a sensation of desire to void until sufficient time has passed for the detrusor to relax (Turner-Warwick, 1979). Isovolumetric contractions, however, give rise to severe pain if the bladder is overdistended (Denny-Brown and Robertson, 1933). In contrast, high pressures can occur in the bladder during micturition, say as a consequence of outlet obstruction, but these pressures do not elicit pain; in these circumstances intravesical pressure may rise to over 90 cm H_2O during voiding, the bladder muscle is often hypertrophied, and the lack of sensation may be due to a change in the compliance of the viscus (see Shah, 1984).

One of the commonest sensory disturbances involving the lower urinary tract is the urge syn-

drome, characterised by either a constant desire to void, or a desire to void at low bladder volumes, and occurring particularly in women. In some of these patients the sensation is associated with involuntary detrusor contractions, whereas in others the sensations are not accompanied by any abnormality that can be demonstrated by bacteriological, radiological, urodynamic or endoscopic investigation (Mundy and Stephenson, 1984). Pain is uncommon in this condition, and the patho-physiological basis of the sensation of urgency is uncertain. In some patients the sensation of urgency occurs when the urethra relaxes and becomes distended, sometimes at low pressure (McGuire, 1984). This aetiology could be associated with the activation of endings outside the urethra itself during the distension that accompanied muscular relaxation. Therefore, the possibility exists that some of the sensations that can be elicited from the lower urinary tract may be due to excitation of localized groups of receptors.

Encoding of events in the visceral domain by spinal visceral afferents

Spinal visceral afferents supplying abdominal and pelvic organs are involved in a variety of functions: neural regulation of continence or evacuation of the bladder or colon, reflexes (viscero-visceral, viscero-somatic) and sensations (painful and non-painful). The messages which trigger these diverse activities must be derived entirely from the information passed to the central nervous system by visceral afferent pathways, and we have to address the problem of how central neurones decode these messages in order to elicit appropriate reflexes, sensations and behaviours. Does any part of the decoding process depend on differentation of visceral afferent neurones with respect to different (adequate) stimuli? Can we, as quasi-objective observers, classify the spinal visceral afferent neurones according to their discharge characteristics and assign them hypothetically to different functions? If not, how are different visceral events encoded by afferents? These questions will now be discussed, and particular attention will be paid to events which are potentially painful.

The spinal cord extracts information about events in viscera by way of (1) the segmental organisation of the afferent inflows from various target organs (see Figs. 3, 4 and 7), (2) the discharge patterns in the visceral afferents initiated by naturally occurring stimuli, and (3) there may be preprogrammed specific synaptic connections between visceral primary afferents and spinal second-order neurones; there may be special biochemical mechanisms (in which the neuropeptides may be involved) which regulate the establishment and maintenance of these functional synaptic connections. The first point is well established and does not require further discussion. The segmental width of the visceral afferent inflow from the organs finds its counterpart in the inaccuracy of the projected true visceral sensations. The third point, as interesting as it may be, is pure speculation and cannot be supported by experimental evidence.

The second point does deserve some special discussion: from the experimental studies which have been reviewed in this paper, it appears likely that the spinal afferent supply to the pelvic and abdominal viscera is, cum grano salis, functionally homogeneous. This may also apply to the spinal visceral afferent innervation of thoracic organs (Malliani, 1982, this volume; see Bahns et al., 1985b). Possibly not included are the afferent fibres of mesenteric Pacinian corpuscles (Gammon and Bronk, 1935), pelvic nerve afferents from the anal canal (Bahns et al., 1985a), lumbar and pelvic afferents from the urethra (Bahns et al., 1985b, 1986a) and thoracic afferents from the oesophagus. These afferent neurones probably serve very special sensory and other functions, and therefore exhibit distinct discharge characteristics to applied stimuli. The function of mesenterial Pacinian corpuscles is presumably concerned with sensing transmitted vibration.

Functional homogeneity means that no subdivision of the visceral afferents into functionally homogeneous types can be made on the basis of

their discharge patterns or other properties, such as the stimulus-response relations to natural stimuli (distension and contraction, see Fig. 6), the distributions of the thresholds to natural stimuli, the ongoing activity, responses to chemical stimuli and the distribution of the conduction velocity of the axons. The studies which have tried to establish a subclassification of spinal visceral afferents into those with nociceptive function and those with other functions (gallbladder: Cervero, 1982; heart: Baker et al., 1980) are probably open to alternative interpretations. Afferents from the gallbladder that respond to high distending pressures may either be the extreme cases of a continuous spectrum of afferent thresholds or their mechanosensitive sites might not have been situated in the wall of the viscus, but close by (see Morrison, 1980; Blumberg et al., 1983; Bahns et al., 1986a,b). The same arguments may apply to the small percentage of spinal visceral afferents from the heart and large thoracic vessels which Baker et al. (1980) claimed to have primarily nociceptive function: these afferents had irregular ongoing activity, high thresholds to mechanical probing and responded vigorously to local application of bradykinin. Though the point of Baker et al. (1980) cannot be refuted, it appears to us that this small fraction of afferents designated as "nociceptive" merely exhibits some minor quantitative differences, in their reactions to the stimuli used, from the so-called "cardiovascular" spinal visceral afferents.

If no functional subclassification of spinal visceral afferents can be made, it must be concluded that the reflexes, regulations and sensations associated with a viscus are produced by the excitation of the same population of visceral afferents, and that no specialised function can be assigned to subpopulations of visceral spinal afferents. This means that these afferents cannot be labelled functionally as "nociceptive" (Baker et al., 1980; Cervero, 1982), "micturition" or "defaecation", etc., but only according to the viscus that is innervated.

A subclassification of visceral receptors based partly on gross anatomy and partly on function has arisen by default, as a result of the historical development of information about visceral afferents; many investigators studied the innervation of individual viscera rather than visceral afferents as a group, and many of the descriptions refer to nerves that sense changes in the state of one viscus. Thus, the movement receptors of the small intestine (Bessou and Perl, 1966), the "in series" tension receptors in the bladder (Iggo, 1955), the specific nociceptors in the biliary tract (Cervero, 1982), the cardiovascular receptors (Malliani, 1982), the renal baroreceptors (Niijima, 1971, 1972, 1975), the adrenal baroreceptors (Niijima and Winter, 1968), the portal venous receptors (Andrews and Palmer, 1967), the renal venous receptors (Beacham and Kunze, 1969), the gastric and mesenteric receptors (Ranieri et al., 1973), and the colonic and retroperitoneal receptors (Blumberg et al., 1983; Bahns et al., 1986a) have been regarded as quite separate functional groups. Indeed, they are separate groups in that they innervate structures with different functions. The differences between receptors that exist in these structures can probably be explained by regional variations in the structures themselves, e.g., in compliance, the amount of smooth muscle present, and the position of receptive endings relative to the viscus will also modify the responses of units. Nevertheless, the results shown in Fig. 6 show a remarkable similarity between the ranges of pressure thresholds of afferents from different abdominal viscera. The unimodal nature of the distribution of thresholds and the fact that the majority of units have stimulus-response functions that cover the normal and supra-normal ranges of visceral pressures point to the existence of a fairly uniform population of receptors in the viscera. No systematic differences appear to exist between Aδ- and C-fibre afferents. Furthermore, the conclusion that there is no substantial evidence for a functional subdivision of spinal visceral afferents means that the specificity theory in its classical sense (see Fig. 1) does not hold for spinal visceral afferents. Therefore, the spinal cord must extract its important information from the intensity of discharge in the visceral primary afferent population. Therefore, we conclude that the "intensity theory" or "summa-

tion hypothesis" (Goldscheider, 1920; see Fig. 1) must be applied to spinal visceral afferents.

Fig. 9 summarises the data on sensory and reflex thresholds to visceral distension in man and the cat, and of afferent thresholds in the cat and ferret. The afferent thresholds are lower than the noxious sensory thresholds, and often less than the reflex thresholds. There is some disagreement in the literature regarding the innocuous and noxious sensory thresholds in the oesophagus and stomach, which are probably due to methodological considerations. However, our overall conclusion from Fig. 9 is that noxious sensations are not due to activation of a specific group of visceral receptors, but to a more intense activation of a population of low-threshold receptors, consistent with the electrophysiological evidence presented earlier.

We do not know the actual neuronal mechanisms of central decoding of visceral afferent activity which leads to different sensations, reflexes and regulations (see Nathan, 1952a; Floyd et al., 1982; McMahon and Morrison, 1982; McMahon et al., 1982; McMahon, this volume; Willis, this volume), but it most probably involves neuronal gating processes (see Morrison, 1982). These gates could be influenced by the intensity of discharge in visceral afferent neurones and by various central influences, such as activity in systems which descend from the brainstem, hypothalamus and telencephalon (Fig. 10) and activity in afferents arising from other structures (see Lumb, this volume). The gating mechanism can hardly be explained in the way that Melzack and Wall (1965) and Wall (1978) explained the generation of cutaneous pain in their "gate control theory". The latter theory presupposes the differentiation of the primary afferent inflow into large and small fibres. This differentiation is missing in the visceral domain. However, the gating mechanisms for visceral functions (sensations, reflexes, etc.) may be influenced by afferent inflows from the skin and deep somatic domain (see Cervero and Tattersall, this volume; Lumb, this volume).

Summary

Functional and morphological properties of spinal visceral afferent neurones supplying abdominal and pelvic organs have been reviewed. These neurones are involved in the regulation of visceral functions, in sensations and in various spinal and supraspinal reflexes. Special emphasis has been placed on visceral nociception and pain. (1) Visceral organs in the thoracic abdominal and pelvic cavities of the cat are supplied by about 22,000–25,000 spinal afferent neurones which amounts to about 1.5–2.5% of the total spinal afferent input. Thus, the density of innervation of the viscera by spinal afferents is small when compared to the density of afferent innervation in the skin and probably in many deep somatic tissues. (2) The spatial resolution of the sensations which can be elicited from the viscera is relatively vague and can be fully explained by the segmental width of the afferent inflow from each viscus. (3) Most spinal visceral afferent units have various common functional properties: they are silent or display a low rate of ongoing activity; their axons are unmyelinated or thinly myelinated (conduction velocity below 2 m/second and mostly below 20 m/second, respectively); their receptive fields consist of from one to nine mechanosensitive sites located in the mesenteries, on the serosal surface or in the walls of the organs; local pressure in their receptive fields elicits slowly adapting responses; they respond to distensions and contractions of the viscera and to stretching of their mechanosensitive endings; they respond to various chemical stimuli applied in their receptive fields. (4) Graded distension and contraction of hollow organs (colon, urinary bladder, gallbladder) lead to graded responses of the visceral afferent neurones. The stimulus-response relationships and distributions of intraluminal threshold pressures for the afferent units show that the thoraco-lumbar and sacral visceral afferents from the hollow organs are largely homogeneous. No distinct population of high-threshold

afferents which would qualify as "visceral nociceptive" could be separated from the whole population of spinal visceral afferents. (5) Afferents from mesenteric Pacinian corpuscles have been excluded from this consideration of visceral afferents. Their function in the viscera is not very well understood, and there is considerable variation in their numbers in different species. Furthermore, spinal afferent neurones that supply the distal parts of the urinary and gastrointestinal tract (urethra and anus), and the oesophagus may show some functional specialisation. (6) The functional homogeneity of the spinal visceral afferent neurones suggests that the same population of afferents encodes various events that give rise to non-nocuous and noxious sensations, a number of reflexes, and to the regulation of viscera. No convincing experimental data exist which justify a subclassification into visceral "nociceptive" and other functional subgroups. It is hypothesised that noxious and innocuous events in the visceral domain are encoded in the intensity of the discharge of the same population of visceral afferent neurones.

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