

Pain

Visceral pain

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Visceral pain is the most common form of pain produced by disease and one of the most frequent reasons why patients seek medical attention. Yet much of what we know about the mechanisms of pain derives from experimental studies of somatic not visceral nociception. The conventional view is that visceral pain is simply a variant of somatic pain, a view based on the belief that a single neurological mechanism is responsible for all pain. However, the more we learn about the mechanisms of somatic and visceral pain, the more we realise that although these two processes have much in common, they also have important differences. Although visceral pain is an important part of the normal sensory repertoire of all human beings and a prominent symptom of many clinical conditions, not much clinical research has been done in this field and there are few clinical scientists with expertise in the management of visceral pain. Instead, visceral pain is usually treated by a range of specialists who take quite different approaches to the management of this type of pain. Thus, the management of visceral pain is frequently unsatisfactory. In this review, we consider visceral pain as a separate form of pain and examine its distinct sensory properties from a clinical perspective. We describe recent research findings that may change the way we think about visceral pain and, more importantly, may help develop new procedures for its management.

Although the precise mechanisms of visceral pain differ between different organs and organ systems, there seem to be two common principles that apply to all visceral pain. The first principle is that the neurological mechanisms of visceral pain differ from those involved in somatic pain, and therefore findings in somatic pain research cannot necessarily be extrapolated to visceral pain. The second principle is that the psychophysics—the perception and psychological processing—of visceral pain also differs from that of somatic pain. The differences between the mechanisms of somatic and visceral pain are not only of scientific interest, but are also relevant to clinical management.

Visceral pain has five important clinical characteristics: (1) it is not evoked from all viscera (organs such as liver, kidney, most solid viscera, and lung parenchyma are not sensitive to pain); (2) it is not always linked to visceral injury (cutting the intestine causes no pain and is an example of visceral injury with no attendant pain, whereas stretching the bladder is painful and is an example of pain with no injury); (3) it is diffuse and poorly localised; (4) it is referred to other locations; and (5) it is accompanied with motor and autonomic reflexes, such as the nausea, vomiting, and lower-back muscle tension that occurs in renal colic (panel).¹ The mechanisms responsible for these clinical features of visceral pain have been reviewed previously.^{1,2}

The fact that visceral pain cannot be evoked from all viscera and that it is not always linked to visceral injury has led to the notion that some viscera lack afferent innervation. We now know, however, that these features are due to the functional properties of the peripheral receptors of the nerves that innervate certain visceral organs and to the fact that many viscera are innervated by receptors that do not evoke conscious perception and, thus, are not sensory receptors in the strict sense. Visceral pain tends to be diffuse because of the organisation of visceral nociceptive pathways in the central nervous system, particularly the absence of a separate visceral

Sensory characteristics of visceral pain and related mechanism

Psychophysics	Neurobiology
Not evoked from all viscera	Not all viscera are innervated by "sensory" receptors
Not linked to injury	Functional properties of visceral "sensory" afferents
Referred to body wall	Viscerosomatic convergence in central pain pathways
Diffuse and poorly localised	Few "sensory" visceral afferents. Extensive divergence in central nervous system
Intense motor and autonomic reactions	Mainly a warning system, with a substantial capacity for amplification

sensory pathway and the low proportion of visceral afferent nerve fibres, compared with those of somatic origin (figure 1).³ The nausea and diaphoresis that accompanies angina is an example of autonomic responses provoked by visceral pain that serve as a warning to the individual to "slow down".

Transmission of visceral pain

In the past few years there have been new insights into the neural mechanisms of the clinical features of visceral pain that have challenged the established paradigm. Traditionally, the two schools of thought among pain researchers were: that the viscera are innervated by separate classes of sensory receptors, some concerned with autonomic regulation and some concerned with sensation, including pain; or that internal organs are innervated by a single and homogeneous class of sensory receptors that at low frequencies of activation send normal regulatory signals and at high frequencies of activation, induced by intense stimuli, signal pain. The first theory extends the concept of nociceptors used in descriptions of somatic pain to the visceral domain.⁴ However, our research and that of others indicates that there are two distinct classes of nociceptive sensory receptors that innervate internal organs.⁵ The first class of receptors have a high threshold to natural stimuli (mostly mechanical). The encoding function—the relation between stimulus intensity and nerve activity—of these high-threshold receptors is evoked entirely by stimuli within the noxious range. To date, high-threshold receptors have been identified in the heart, vein, lung and airways, oesophagus, biliary system, small intestine, colon, ureter,

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urinary bladder, and uterus.^{6,7} The second class of receptors are intensity-encoding receptors that have a low threshold to natural stimuli (again mostly mechanical) and an encoding function that spans the range of stimulation intensity from innocuous to noxious. These receptors constitute a homogeneous category of sensory receptors that encode the stimulus intensity in the magnitude of their discharges—intensity-encoding receptors have been described in the heart, oesophagus, colon, urinary bladder, and testes.^{6,7}

Another theory is that a large component of the afferent innervation of internal organs consists of afferent fibres that are normally unresponsive to stimuli and become activated only in the presence of inflammation.⁴ According to this theory, these so-called silent nociceptors are functionally different from the rest of visceral afferent fibres and are mainly concerned with stimuli such as tissue injury and inflammation, rather than with mechanical stimuli such as stretch. One proposition is that this new class of sensory receptors contributes to the signalling of chronic visceral pain, to long-term alterations of spinal reflexes, and to abnormal autonomic regulation of internal organs. We believe that the clinical importance of these silent nociceptors and their role in visceral pain remains to be established. It is clear, for example, that there are not as many silent nociceptors as were initially thought: they comprise no more than 40–45% of total afferent visceral innervation of the colon and bladder,⁷ not the 80–90% estimated by other researchers.^{8,9} In addition, the finding that these afferents can be sensitised does not necessarily mean that they have a nociceptive role, least of all in the viscera where heightened sensitivity to internal stimuli is required for adaptation of many normal homeostatic processes.

The strongest evidence indicates that high-threshold receptors and intensity-coding receptors contribute to the peripheral encoding of noxious events in the viscera.⁴ Brief acute visceral pain, such as acute colonic pain or pain produced by an intense contraction of a hollow organ, could be triggered initially by the activation of high-threshold afferents. More extended forms of visceral stimulation, including those of hypoxia and tissue inflammation, result in the sensitisation of high-threshold receptors and bring into play previously unresponsive silent nociceptors. Once sensitised, these nociceptors will begin to respond to the innocuous stimuli that normally occur in internal organs. As a consequence, the central nervous system receives an increased afferent barrage from peripheral nociceptors that is initially due to the acute injury but that, for the duration of the inflammatory process, is also influenced by the physiological activity of the internal organ and which persists until the process of peripheral sensitisation subsides completely. This barrage, in turn, triggers central mechanisms that amplify and sustain the effect of the peripheral input. In this way, the pain is intensified and its duration extended by a central mechanism brought into action by the peripheral barrage.

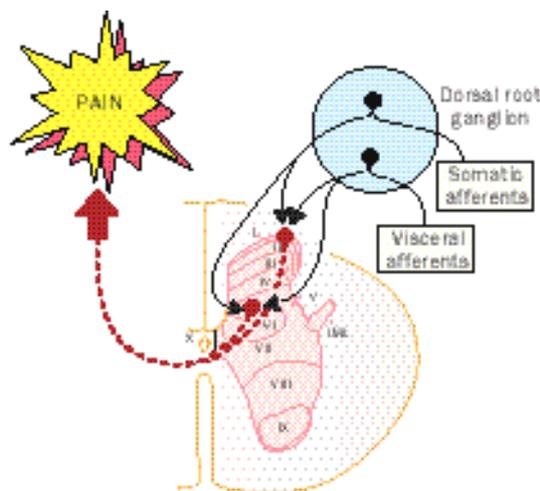


Figure 1: **Viscerosomatic convergence of primary afferent fibres on neurons of lamina I and lamina V of dorsal horn**
IML=intermediolateral cell column.

Furthermore, damage and inflammation of the viscera also affects its normal pattern of motility and secretion, which produces dramatic changes in the environment that surrounds the nociceptor endings. The altered activity of the viscera further increases the excitation of sensitised nociceptors and may even be sufficient to excite more distant nociceptors not affected by the initial insult.¹⁰

Since visceral nociceptors are not easily excitable under normal conditions, afferent discharges due to viscous activity after an injury or inflammation may be greater in magnitude and duration than the discharges produced by the acute injury, which potentially

makes the central effects of discharges after injury even greater than those of the initial insult. Thus, visceral pain may persist even after the initial injury is on its way to resolution.

Biochemistry of visceral pain

There are two distinct biochemical classes of fine calibre unmyelinated primary afferents that innervate somatic and visceral tissues: the first class contain neurones that express peptide neurotransmitters, such as substance P and calcitonin-gene-related peptide (CGRP); and the other class does not express these substances.¹¹ These two classes can also be distinguished by various enzymes, such as fluoride-resistant acid phosphatase found in the non-peptide group, and receptors, such as the nerve-growth-factor receptor tyrosine kinase A, that are expressed by one class but not the other. The two classes also differ with regard to the trophic requirements needed to maintain their normal phenotypes and anatomical differences in their termination patterns in the grey matter of the spinal cord. The peptide-containing afferents of the somatic system terminate in the outermost layers of the posterior horn, lamina I, outer lamina II, and lamina V, whereas the non-peptide groups terminate in inner lamina II.¹¹

Somatic fine afferent fibres include both biochemical classes, but the functional role of these two classes in somatic pain is unclear. By contrast, most visceral afferent fibres, seem to belong to the peptide class that express peptide neurotransmitters^{12,13} and do not express carbohydrate groups characteristic of the non-peptide class. In addition, as with somatic peptide-containing afferents, visceral afferents also terminate on spinal cord lamina I and lamina V. The biochemical identification of visceral afferents as part of the peptide-containing class has important implications for the future development of therapy for visceral pain, because it suggests that peptides are particularly important in the transmission of information from the viscera. In our laboratory, for example, we have found that transgenic mice that lack the receptor for substance P do not develop hyperalgesia after visceral inflammation (figure 2), whereas they do develop hyperalgesia after inflammation of somatic tissues. Our findings indicate that substance P may have a specific role in visceral hyperalgesia (unpublished data). Several receptor antagonists for substance P are currently under clinical development and may prove effective for the treatment of visceral pain and hyperalgesia.

Wind up: central-nervous-system changes due to visceral afferent signals

Nociceptive afferent discharges in visceral afferents can evoke profound changes in the central nervous system; for example, repetitive noxious stimulation of the viscera evokes increases in the excitability of viscerosomatic neurons in the spinal cord.¹⁴ Such changes are highly selective and organised such that they occur on only those viscerosomatic cells that are driven by the conditioning visceral stimulus. In somatic nociceptive systems, a common correlate of the increased excitability is the frequency-dependent increase in neuronal excitability which is known as wind up.

The phenomenon of wind up is generally regarded as a display of central sensitisation, but visceral-somatic spinal nociceptive neurons, which are capable of showing increased excitability on repetitive noxious stimulation, do not wind up as somatic neurons do,¹⁵ which shows once again the differences between somatic and visceral nociceptive systems and also casts some doubt on the role of wind up as a generator of central sensitisation and hyperalgesia. Instead, the increases in excitability of spinal-cord nociceptive neurons induced by repetitive noxious stimulation may be due to the properties of the neuronal networks activated by the stimuli, to the release of certain transmitters, or to both. Increased excitability could be mediated by positive feedback loops between spinal and supraspinal structures. These loops are particularly prominent on visceral nociceptive neurons¹⁶ and could be responsible for the enhanced motor and autonomic reflexes that frequently accompany visceral pain states, such as the nausea, increased abdominal muscle tension, and hunched posture in appendicitis. The postsynaptic actions of the neurotransmitters released by noxious stimuli can also contribute to the increased excitability of visceral nociceptive pathways after long periods of stimulation.

Central pathways that transmit visceral pain

The traditional view of the transmission of visceral and other types of pain is that signals are carried by crossed anterolateral pathways, mainly the spinothalamic and spinoreticular tracts. This theory, however, has been challenged by the discovery of three previously undescribed pathways that carry visceral nociceptive information: the dorsal column pathway, the spino(trigemino)-parabrachio-amygdaloid pathway, and the spinohypothalamic pathway.

The experimental evidence for the importance of the dorsal column pathway in the transmission of visceral nociceptive information is compelling.¹⁷⁻¹⁹ Data from studies in laboratory animals have direct implications for medical practice, either as an explanation for previously unexplained findings, such as whole body pain relief by C1 commissural myelotomies, or as a basis for new surgical interventions.²⁰ Other important data relate to the transmission of visceral nociceptive information via the parabrachial nucleus and the amygdala^{21,22} and directly from the spinal cord to certain hypothalamic nuclei.²³ These new findings are being incorporated into clinical and surgical practice, but only time will tell the exact contribution of each of these new pathways to the perception of visceral pain.

These data have also reopened an old argument about the existence of a true "pain pathway", as opposed to the notion that pain is the result of patterns of activity that arise in non-specific pathways and nuclei. The sensation of

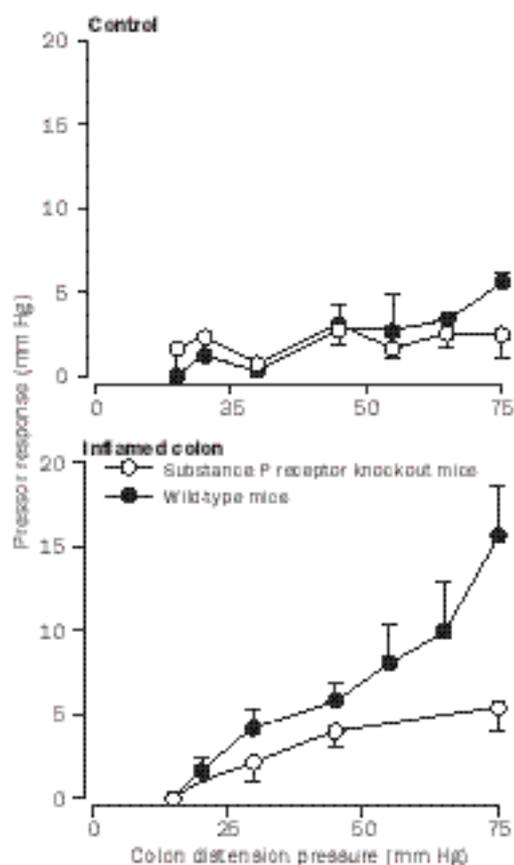


Figure 2: **Cardiovascular reflex responses to graded distension of colon in anaesthetised mice, before and after inflammation of mucosa by acetic acid**

In mice that express normal substance P receptors (wild-type mice), induction of colon inflammation increased responses to colon distension or visceral hyperalgesia. By contrast, in transgenic mice with disrupted substance P receptor (knockout mice), there is a normal stimulus response curve in control conditions but no change in responsiveness after inflammation of colon.

pain is a complex experience with multiple facets, so, in our view, it is not surprising to find that many areas of the central nervous system are involved in its processing. There are, for example, descriptions of responses to visceral sensory signals in neurons in the visual cortex that emphasise the convergent nature of most sensory messages but do not deny the primary role of the visual cortex in visual perception.²⁴ In general, however, notions of the nervous system built upon hypothetical patterns of unspecified connections between distant areas of the brain have not provided researchers and clinicians with useful ways to approach scientific questions.

New techniques for study of visceral pain

New electrophysiological and imaging techniques have advanced our understanding of visceral pain perception. Microstimulation of the thalamus, for example, can evoke visceral pain experiences, such as angina or labour pain, sometimes years after the original episode.^{25,26} These observations highlight the integrative role of the thalamus in processing memories of pain and the existence of long-lived neural mechanisms that are capable of storing the results of a previous painful experience for many years. The pain memories evoked in these studies are of visceral pain, presumably because they are common in the general population and tend to be fairly intense experiences.

Other studies have used imaging techniques to map active sites in the brain after experimentally induced or clinically evoked visceral pain. Silverman and colleagues' positron-emission-tomography study²⁷ of the cerebral representation of enteric pain showed that in healthy volunteers acute noxious stimulation of the rectum evoked brain activity in the anterior cingulate cortex, a region associated with the perception of the affective or emotional qualities of the pain experience. The precise components of the cingulate cortex activated by the visceral stimulus differ from those normally activated by somatic stimulation and correspond to areas of the brain that are involved in visceromotor reactions and emotional vocalisations in primates. Silverman and colleagues also examined patients with irritable bowel syndrome who showed different patterns of brain activation than those seen in the healthy volunteers.²⁷ Activity in the anterior cingulate cortex did not increase in these patients, instead, the dorsolateral prefrontal cortex was activated—in expectation of the visceral stimulus. This finding is consistent with the hypervigilance to visceral events that is characteristic of patients with irritable bowel syndrome.

Putting research into clinical practice

Most clinical specialists continue to treat visceral pain as just a symptom and not as a distinct neurological entity. Whether or not their patients will obtain effective pain relief will depend on the views of each specialist towards the management of pain. However, it is likely that the findings of basic research into visceral pain will soon start to have an effect on clinical thought and practice. This process is already happening in the management of so-called functional abdominal pain syndromes, which include irritable bowel syndrome, functional dyspepsia, and other conditions characterised mainly, and sometimes exclusively, by abdominal pain unrelated to a clear pathology of the gastrointestinal tract. For example, the findings of studies with positron emission tomography lend support to the hypothesis that these syndromes may be the result of visceral hypersensitivity that causes patients to become more aware of gastrointestinal activity.^{27–32} This heightened awareness may be the result of sensitisation of the peripheral nociceptors or of alterations of central processing that lead to increased activation of visceral nociceptive pathways. In either case, the findings indicate that these patients could be treated with compounds that reduce peripheral or central sensitisation (serotonin-receptor blockers for the former, N-methyl-D-aspartate-receptor blockers for the latter). Much research into this area of visceral pain is underway and promises to provide definitive answers and more effective approaches to the difficult clinical issue of functional abdominal pain. We hope that the progress made in this area will encourage clinicians in other specialties to begin to build working relationships with basic researchers in our search for new treatments for visceral pain.

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