Visceral pain—central sensitisation

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Visceral pain is the most common form of pain produced by disease and one of the most frequent reasons for patients to seek medical attention. Yet much of what we know about the basic mechanisms of pain derives from experimental studies of somatic nociception. This would be justified if the mechanisms of somatic and visceral pain were similar so that information obtained by studying one form of pain could be extrapolated to interpret the mechanisms of the other. However, the more we know about the mechanisms of somatic and visceral sensation the more we realise that these two processes, while having many common features, also have important differences. We seldom have any sensory experiences from our internal organs other than pain and discomfort and even when other sensations occur, such as bladder or stomach fullness, these can easily evolve towards pain if the stimulus persists.

The five main characteristics of visceral pain—that is, those clinical features that make visceral pain unique—are that visceral pain:

(i) is not evoked from all viscera,
(ii) is not linked to visceral injury,
(iii) is referred to other locations,
(iv) is diffuse and poorly localised, and
(v) is accompanied by motor and autonomic reflexes.

Properties (i) and (ii) generated the notion that some viscera lacked an afferent innervation. We now know that these features of visceral pain are due to the functional properties of the peripheral receptors that innervate different visceral organs and to the fact that many viscera are innervated by receptors whose activation does not evoke conscious perception and that are not “sensory” receptors in the strict sense. Properties (iii), (iv), and (v) relate to the central organisation of visceral nociceptive mechanisms, particularly to the lack of a separate visceral sensory pathway and to the low proportion of visceral afferent fibres compared with those of somatic origin.

However, central mechanisms are clearly dependent on peripheral afferent drives. We have recently observed that induction of artificial ureteric calculi in rats results in a marked change in the pattern of ureteric motility. This is characterised by a large increase in the amplitude of contractions, such that they increase from a mean of about 5–10 mm Hg, well below the nociceptive threshold in normal humans and animals of 20–25 mm Hg, to values around this level. In patients with ureteric calculi, pain and hyperalgesia often last for some time after elimination of the stone. Peripheral mechanisms may be responsible for this phenomenon as we also found the same changes in ureteric motility in rats that spontaneously eliminated the artificial stone during the 1–8 day survival period between stone induction and recording.

Noceptive afferent discharges in visceral afferents evoke profound central changes. Prolonged noxious stimulation of the visceral pain evokes increases in the excitability of viscerosomatic neurones in the spinal cord. Such changes are very selective and highly organised as they occur only on those viscerosomatic cells that are driven by the conditioning visceral stimulus. In somatic nociceptive systems, a common correlate of the enhanced excitability is the frequency dependent increase in neuronal excitability known as “wind up”.

The phenomenon of wind up is generally regarded as a display of central sensitisation. However, visceral nociceptive neurones, which are quite capable of showing increased excitability on prolonged noxious stimulation, do not “wind up” as somatic neurones do, thus demonstrating again the differences between somatic and visceral nociceptive systems and casting doubt on the role of “wind up” as a generator of central sensitisation and hyperalgesia.

The increases in excitability of spinal cord noceptive neurones induced by repetitive noxious stimulation may be due to the properties of the neuronal network activated by the stimuli or to release of certain transmitters, or both. Excitability increases could be mediated by positive feedback loops between spinal and supraspinal structures. These loops are particularly prominent on visceral nociceptive neurones and could be responsible for the enhanced motor and autonomic reflexes that frequently accompany visceral pain states. The postsynaptic actions of the neurotransmitters released by noxious stimuli can also contribute to the enhanced excitability of visceral nociceptive pathways following periods of prolonged stimulation.

Glutamate is a major transmitter in the spinal cord, and the N-methyl-D-aspartate (NMDA) glutamate receptor subtype has been proposed as having a particular role in mediating persistent pain and hyperalgesia in the spinal cord. In a recent study from our laboratory, we observed a differential effect of NMDA receptor antagonists on the reflex responses in anaesthetised rats to acute noxious stimuli applied to normal somatic and visceral tissue. While the responses to graded noxious stimulations of the ureter were dose dependently inhibited by the NMDA receptor ion channel blocker ketamine, the responses to graded pinch stimuli of one hindpaw were not affected. We believe that acute noxious stimulation of normal visceral tissue provokes

Abbreviations used in this paper: NMDA, N-methyl-D-aspartate; NK, neurokinin.
intense responses that recruit neural mechanisms mediated by NMDA receptors, whereas in somatic pathways these mechanisms are recruited only by an enhanced peripheral input such as that produced after injury or inflammation.

Substance P has long been thought to be involved with nociceptive processing as it is expressed in small diameter primary afferents, most of which are connected to peripheral nociceptors. However, the published data on the effects of neurokinin (NK) 1 receptor antagonists in phase 3 pain in animal models is somewhat contradictory. The recent development of mutant mice strains with disruptions of the gene coding for the NK1 receptor has provided an alternative method to investigate the role of substance P and NK1 receptors in pain.1 Data from experiments using receptor antagonists and from experiments in mutant mice suggest that the role of substance P and the NK1 receptor is particularly important in persistent visceral pain, especially that with a neurogenic component.

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