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"I would have everie man write what he knowes and no more."—Montaigne

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Editorial I

Gate Control Theory of pain stands the test of time

In 1965, Pat Wall (who died August 8, 2001) and Ron Melzack published their paper in *Science*, entitled a 'New Theory of Pain'.[1] Despite the mention that it was a theory, endless arguments and debates ensued. Poring over the details, arguing over the substrates, all futile and pointless since the theory has stood the test of time and has changed the way we think about pain—the new theory has endured.

Why? The theory simply stated, in an elegant and succinct way, that the transmission of pain from the peripheral nerve through the spinal cord was subject to modulation by both intrinsic neurones and controls emanating from the brain (Fig. 1). Pat then went on to add to and refine the theory to include changes in afferents, prolonged central excitability, and changes in these systems after nerve damage. The action of the gate control showed it to be subtle and far beyond a simple control of overall excitability. Excitations and inhibitions are independently controlled. Different types of convergent afferent activity may be turned on and off. There are signs of both short- and long-lasting actions. Now, over the past 10 yr, we have gathered more and more information about the transmitters, receptors and channels involved in the transmission and control of noxious messages. From this knowledge, there are potential new targets for analgesic therapy,[2] and a rationale on which to base the use of opioids and other analgesics. We now have more experimental drugs available, which allows us to study the roles of transmitters and receptors in physiological events. There are numerous animal models for clinical pain states such as inflammation and neuropathies, and these models have shown that several transmitter systems that have minor actions in acute pain can play important roles in more persistent pain.[3] It is a salutary experience to think back to 1960, when the electrophysiological, anatomical, neurochemical, molecular and other techniques that have shed so much light into the events that underlie pain, were only just appearing. The theory was a leap of faith but it was right! The concepts of convergence and modulation reduced the emphasis on destruction of pathways and led to the idea that pain could be controlled by modulation—reduce excitation or increase inhibition.

The Gate Theory of pain has made us think since about changeable transmission. This plasticity, the capacity of pain signalling and modulating systems to alter in different circumstances, has changed our ways of thinking about pain control. Signalling events are not fixed, and are not the same in all situations but are subject to alteration.[3]

So where have we gone through the Gate? A long way! The Gate Theory did not emphasize peripheral processes since the aim was to propose how the central nervous system dealt with sensory inputs. We now know that other than physiological pain, the main clinical pains arise from damage to tissue (inflammatory pain), whereas neuropathic pain results from changes in damaged nerves. However, both cause profound changes in the spinal cord and the brain. We now believe that all persistent pains exhibit plasticity in that the peripheral and central signalling mechanisms can alter. Indeed, changes in areas adjacent to those directly influenced by, for example, nerve injury can occur. Peripheral changes drive central compensations and adaptations, so that the mechanisms involved in the pain are likely to be multiple and located at a number of sites. When tissue is damaged, peripheral chemicals sensitize the sensory endings and after neuropathic pain, excitability changes occur within the nerve itself. These peripheral changes then alter activity in central systems.[4]

Marked central changes are likely even when a neuropathy arises from purely peripheral origins. Aberrant processing of sensory information leading to hyperalgesia, and allodynia suggests central compensation, as does the simple consideration that damage to a nerve would be expected to cause sensory loss, not increased pain. It is

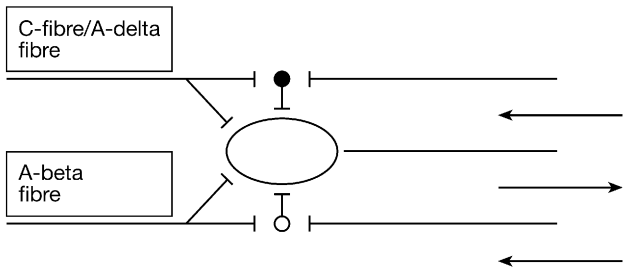

Fig 1 The Gate Theory proposed that small (C) fibres activated excitatory systems (black neurone) that excited output cells—these latter cells had their activity controlled by the balance of large-fibre (A-beta) mediated inhibitions and were under the control of descending systems.

possible that increased central hyperexcitability is a maladaptive compensation for the marked loss of peripheral input that occurs after nerve injury.[5] The Gate Theory provided a framework for examining the interactions between local and distant excitatory and inhibitory systems in the dorsal horn and this has produced thousands of studies.

What are the central mechanisms of pain? Inflammation will produce peripheral sensitization[6] in that the system will be driven harder for a given stimulus. Ongoing ectopic activity in damaged peripheral nerves will continually produce transmitter release into the spinal cord, and this will cause subsequent neuronal activity.[3 5 6] After tissue and nerve injury, there are increases in the activity of calcium channels within the spinal cord responsible for both presynaptic transmitter release and postsynaptic neuronal excitability. N-type calcium channels, in particular, become more active and contribute to activity evoked by both low- and high-threshold peripheral stimuli. Furthermore, following nerve injury, there is an upregulation of the $\alpha 2\delta$ subunit of calcium channels, suggesting a greater number of channels are active at any one time. These findings have relevance to the mode of action of the drug, gabapentin, used in neuropathic pain, since gabapentin binds to this component of calcium channels, where it can be presumed to act as an antagonist. Active calcium channels also produce release of glutamate and peptides into the spinal dorsal horn during inflammation.[7]

Thus, as there is augmented transmitter release, an increased release of glutamate, the major transmitter in afferent A- and C-fibres, is likely, and this has been shown to occur in the human spinal cord of patients after nerve injury. Increased glutamate then leads to enhanced activation of the receptors for glutamate, especially the N-methyl-D-aspartate (NMDA) receptor implicated in wind-up and central sensitization.[3] Central sensitization occurs when peripheral sensory neurone activity drives central spinal systems that amplify and prolong the incoming sensory messages. Consequently, this is a mechanism whereby the final sensation of pain becomes dissociated from peripheral activity. One manifestation of central sensitization is wind-up where repeated constant C-fibre stimulation elicits increased spinal neuronal responses in animals and pain reports in patients. As spinal neurones become more excitable, their receptive fields expand and this is thought to be a major factor in secondary hyperalgesia.[4]

Glutamate is believed to be a key transmitter in central sensitization. In the spinal cord it appears to play a pivotal role, in concert with peptides, in determining the level of pain transmission. In the dorsal horn, metabotropic, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors for glutamate have distinct actions. The AMPA receptor sets the baseline level of activity and when activated, the NMDA receptor then causes wind-up. This enhances and prolongs transmission and so has been implicated in many states of central hypersensitivity, including hyperalgesia and allodynia seen in postoperative, inflammatory and neuropathic pains. There is a clear consensus that the NMDA receptor is only activated when the intensity and duration of the noxious stimulus exceeds a certain level. This process probably includes excitatory peptide actions at their receptors, removing the magnesium block of the NMDA receptor channel.[8]

Antagonists at multiple sites on the NMDA receptor complex, including the licensed channel blocking drug, ketamine, have been shown to be effective not only in a number of animal models but also in patients. The therapeutic window for NMDA receptor antagonists may be improved by use of subtype-specific drugs as there are four subunits of the receptor. The NR2B subtype of the receptor, for example is an interesting target since it has a restricted distribution yet antagonists appear to be effective in reducing nociception.[8]

Further mediators, including prostanoids and the gas nitric oxide, are produced spinally by NMDA receptor activation and appear to act to further enhance pain signalling. Block of the production of nitric oxide abolishes wind-up and reduces hyperalgesia. By contrast, adenosine also appears to be released by NMDA receptor activation but then acts as a negative feedback to damp down activity in the system.

Controversy exists regarding the role of inhibitory systems—opioids may not be fully effective in some patients with neuropathic pain. The issue may simply be that neuropathy leads to a reduction in opioid sensitivity that can be overcome by dose escalation *if* excessive side-effects do not occur. Why opioid therapy might be less effective is unclear—no marked changes in opioid receptors or levels of anti-opioid peptides are seen. Spinal application of opioids may be a sensible approach because it allows high doses to be given locally. However, following tissue damage there are increases in the effectiveness of morphine which is thought to be due to reductions in the peptide CCK, which acts as an anti-opioid. Antagonists of CCK may be useful drugs as adjuncts to morphine when the opioid has reduced effectiveness.[3]

Likewise, complex changes in intrinsic gamma amino-butyric acid (GABA)-mediated inhibitions and in the monoamine containing inhibitory pathways descending from the brain to the spinal cord have been described. Some reports suggest a reduction in tissue levels of GABA, but this may suggest increased release. Cannabinoids may be a novel approach, but we await clinical data on their effectiveness in neuropathic and other pains. The CB1 receptor is present in the spinal cord, and when activated, mediates analgesia. Whether this changes after tissue or nerve injury is unknown.

A better understanding of the multiple mechanisms contributing to neuropathic and inflammatory pain should lead to a more effective use of existing drugs and provide a

basis for the development of potential new therapies.[2 9] The Gate remains open. . . but there are more ways of shutting it.

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