limited by sedation, bradycardia and hypotension. Cholinergic agonists (neostigmine) enhance noradrenergic-mediated analgesia. Midazolam produces segmental spinal analgesia, probably via the benzodiazepine receptor, which forms a complex with the GABA receptor.

Supraspinal level

The supraspinal function in nociception is beginning to be explored with the advent of non-invasive imaging, such as functional MRI and positron emission tomography. The perception of pain is associated with changes in activity of the thalamus, primary and secondary cortex and particularly the anterior cingulate cortex.

Various regions of the brain are involved with descending inhibition (Figure 3). These pathways originate at the level of the cortex and thalamus, and are mediated via relay stations in the brainstem, such as the periaqueductal grey matter, nucleus raphe magnus and locus coeruleus subcoeruleus complex. The inhibitory pathway then descends the spinal cord via the dorsal columns and terminates at the dorsal horn where neurotransmitters (noradrenaline, 5-HT) and the endogenous opioids are released to provide antinociception. All three receptors (mu, delta, kappa) play a role in the ascending pathways but the mu and delta receptors are mainly responsible in the descending component.

Noradrenaline and 5-HT synthesis and release are increased by opioids, and they in turn enhance the action of opioids. This may be the mechanism by which the antidepressants and tramadol work as analgesics.

Psychology

It is inappropriate to see pain as either physical or psychological; it is always both, as stated in the IASP definition. Pain sometimes occurs without apparent cause or does not occur despite obvious injury (e.g. in a wounded soldier on the battlefield). It can persist after tissue healing or fail to respond to appropriate treatments. An example of this is the placebo response, whereby a 'sham' treatment can produce good analgesia. The converse of this is the nocebo response where pain can be experimentally induced despite there being no nociceptive stimulus, only a suggestion of one.

The pain experience and amount of suffering depend on many psychological variables such as: anxiety; past experiences; the meaning to the patient of the pain, injury or illness; their beliefs about treatment and medications (fear of dependence, addiction, tolerance, organ damage); and self-management strategies. This applies equally to acute as it does to chronic pain. Pain services should screen patients to address any critical psychological issues as an integral component of appropriate medical management. Motivation and positive attitudes can be just as important to pain control and recovery. ◆

FURTHER READING

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Neurobiology of chronic pain states

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This article focuses on the sensory systems involved in pain perception and how they may be altered in chronic pain states; it concentrates on nerve-injury-related changes. Other factors may also play a significant role in determining the experience of pain, level of distress and functional disability (Figure 1). Woolf made a distinction between acute, 'physiological' pain and chronic 'pathological' pain (Figure 2). However, acute factors potentially play a major role in initiating the peripheral and central changes required for the development of chronic pain.

Research over the last few decades has shown that many changes in the peripheral and central nervous system contribute to the development and maintenance of chronic pain. The challenge to clinicians is whether improved understanding of neurobiology can be translated into prevention or more effective treatment of chronic pain.

Figures 3 outlines the pathways involved in pain processing. In chronic pain, specific changes can be detected in the nervous system, depending on whether nerve damage or a continuing inflammatory response is the main component of the syndrome.

Peripheral alterations

Following nerve injury, two major changes occur peripherally in sensory neurons: alterations in the electrical response properties and alterations in the chemical nature of the neurons.

Electrical properties

Spontaneous activity: normally, a peripheral stimulus (e.g. pin prick) is required to activate peripheral nociceptors. Neuronal sodium channel permeability increases, resulting in action potential generation and propagation. After nerve injury, action potentials

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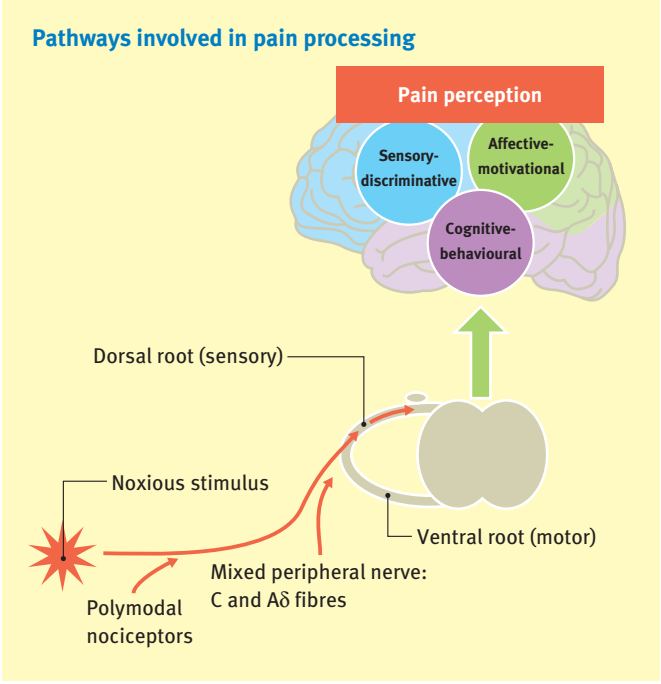

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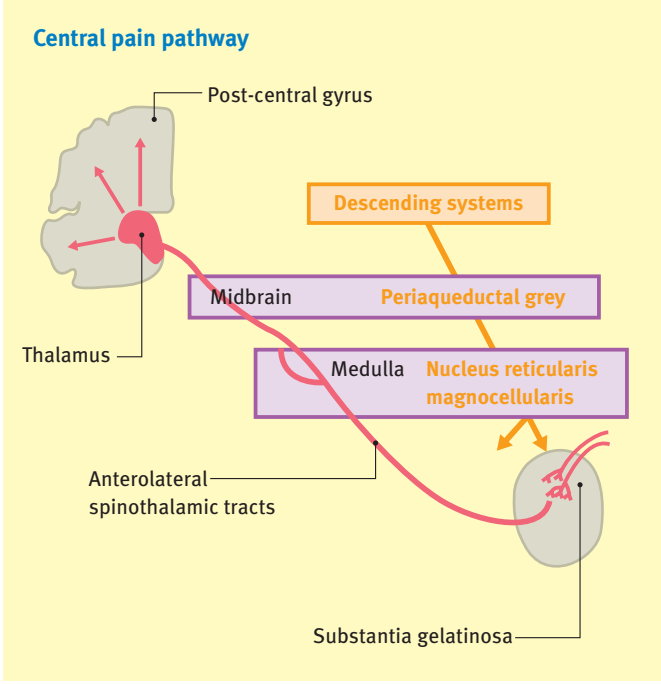

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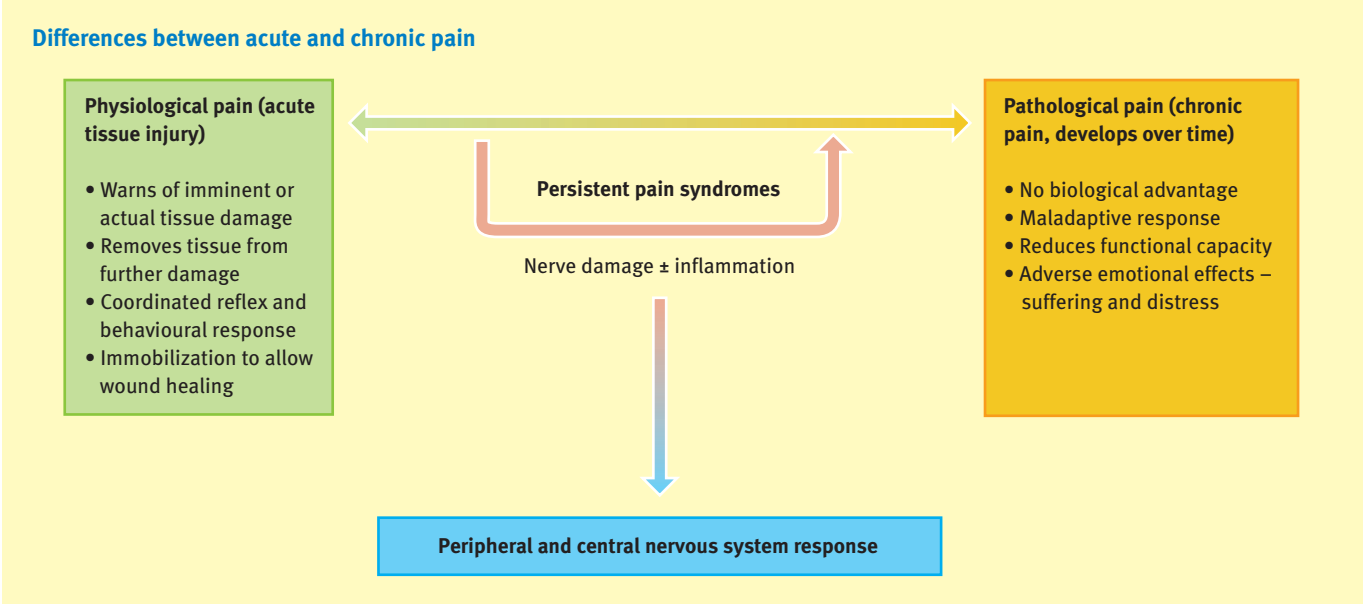
arise spontaneously at sites distant from peripheral nociceptors, in the absence of any peripheral stimulation. Both the injured neuron and surrounding non-injured neurons may be involved, with the phenomenon being more marked in A than in C fibres. These spontaneously arising action potentials, or 'ectopic discharges', can originate from the nerve injury site, and more proximally, at the cell bodies themselves, in the dorsal root ganglia. Several factors are important in the generation of these ectopic discharges. There is an upregulation of voltage-gated sodium channels. The subtype of sodium channel depends on sensory fibre type. Tetrodotoxin-sensitive $Na_v1.3$ is found mainly in the embryonic nervous system, but it is upregulated after nerve injury, and plays a role in ectopic impulse generation. Downregulation of potassium channels occurs after nerve injury. There is also a decrease in the activation threshold of heat-sensitive channels, such that they may be activated at body temperature. Animal models and clinical microneurographic work have shown that the rate of ectopic discharges may be related to the severity of spontaneous pain.

Evoked activity: normally a high-intensity peripheral stimulus is required to initiate an action potential in nociceptors. It is propagated centrally along small myelinated Aδ fibres and unmyelinated C fibres. The initiation of action potentials stops when the stimulus has ceased. Mechanical stimulation of the sensory axon distant from peripheral nociceptors does not generate action potentials. In contrast, after nerve injury, there may be continued action



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