Recent concepts in the neurophysiology of pain

A. Wright

School of Medical Rehabilitation, Faculty of Medicine, University of Manitoba, Canada

SUMMARY. This paper describes many of the processes that exist for upregulation of the nociceptive system in response to tissue injury. The processes of peripheral and central sensitization are described. Potential interactions between the nociceptive, motor and autonomic systems are considered. The potential for psychosocial factors to influence neuroplasticity within the nociceptive system is also discussed. © 1999 Harcourt Publishers Ltd.

INTRODUCTION

In clinical practice we are well aware of the impact of pain on an individual. We see people rapidly transformed from a situation in which they are experiencing no pain or minimal levels of pain to a situation in which their pain experience is so severe and pervasive that it drives all of their behaviours and becomes the central focus of their existence. Examples of patients who have sustained a whiplash injury or other significant musculoskeletal trauma provide an indication of the impact of pain on previously pain free individuals. The level of change that occurs in the behaviour of these individuals implies a very marked upregulation of nociceptive system function and consequent upon this, enormous neuroplasticity and change in many aspects of central nervous system (CNS) function. It has become abundantly obvious that factors other than the injuring stimulus influence pain perception and that many psychosocial factors can contribute to the neuroplasticity that occurs in response to an initial pain stimulus.

Over the last 20 years, an increasing body of research has developed describing the ways in which nociceptive system function can be upregulated, and pointing to the effects of upregulation of the nociceptive system on somatomotor and somatosympathetic function.

The nociceptive system is normally a very quiescent system requiring strong, intense, potentially damaging stimulation before it becomes activated. Yet, once an individual is experiencing pain, relatively innocuous stimuli activate the system and trigger pain perception. This altered perceptual state is encompassed by the phenomenon of hyperalgesia, an exaggerated or increased response to a noxious stimulus, and the related phenomenon of allodynia, the production of pain by a stimulus that would not normally be painful (IASP 1986). These phenomena have been the subject of numerous research studies since the 1930s (Lewis 1936; Hardly et al. 1950; Meyer et al. 1985; Torebjork et al. 1992; Willis 1992).

PERIPHERAL SENSITIZATION

Many early studies pointed to sensitization of peripheral nociceptors as a mechanism underlying the increased sensitivity to subsequent stimulation that takes place following tissue injury. It is apparent that many peripheral nociceptors are polymodal in the sense that they respond to chemical as well as mechanical and thermal nociceptive stimulation (Kymazawa 1996). It is also apparent, from a large number of studies on both humans and animals, that chemical mediators released into the tissues as a result of tissue injury promote sensitization of peripheral nociceptors. Some of the key mediators, which have been identified, include bradykinin, serotonin, histamine, potassium, adenosine, protons, prostaglandins, leukotriennes and cytokines (Dray 1995). The effects of these mediators involve binding to specific receptors, activation of ion channels for depolarization, activation of intra-cellular messenger systems, release of a range of neuropeptides to promote neurogenic inflammation and alteration of...
neuronal properties by modifying gene transcription. (Dray 1995; Bevan 1996). A number of receptors and second messenger systems may be activated following the release of different inflammatory mediators (Mizamura & Kumazawa 1996). While polymodal receptors respond to a range of stimuli, it is apparent that different receptors and second messenger systems are involved in excitation and sensitization for different stimulation modalities (Mizamura & Kumazawa 1996). One of the most fundamental influences on nociceptor sensitivity is the pH of the surrounding tissue. High local proton concentrations are known to occur in many inflammatory states and the consequent reduction in pH can contribute to sensitization of polymodal nociceptors (Handwerker & Reeh 1991; 1992; Reeh & Steen 1996). Altered pH of the local chemical environment of peripheral nociceptors is a particularly important factor in inducing mechanical sensitization and ischaemic pain (Steen et al. 1992, Dray 1995). Combinations of inflammatory mediators and combinations of chemical mediators with altered tissue pH appear to be more effective in inducing sensitization than individual chemical mediators alone (Handwerker & Reeh 1991). Thus, in the natural situation it appears to be a combination of chemical mediators, which Handwerker and Reeh have referred to as ‘an inflammatory soup that produces sensitization of peripheral nociceptors’ (Handwerker & Reeh 1991).

It is also clear that endogenous chemicals act on a variety of receptors, activate a number of different intracellular second messenger systems and influence different ion channels (Dray 1995; Mizamura & Kumazawa 1996). It is therefore possible for nociceptors to exhibit different forms of sensitization and for distinctions to be made between the processes leading to thermal, mechanical and chemical sensitization (Mizamura & Kumazawa 1996). For example, prostaglandins may induce sensitization to chemical mediators at much lower concentrations than those required to induce sensitization to heat stimuli (Mizamura & Kumazawa 1996).

Sensitization can also be produced through a number of different mechanisms. It can occur as a result of a direct influence of mediators such as protons and serotonin on membrane ion channels, particularly sodium channels, to increase membrane permeability and cellular excitability (Dray 1995). Many mediators act indirectly via G proteins and a variety of second messengers to induce changes in membrane ion channels. Adenosine, bradykinin, serotonin and prostaglandins may act on receptors that produce changes in potassium ion permeability (Dray 1995).

It is also apparent that kinins such as bradykinin act on the B2 receptor that is coupled to a G protein causing phospholipase C activation amongst other effects. This leads to the release of intracellular calcium and activation of ion channels to increase membrane permeability, particularly for sodium and calcium ions (Dray 1995). Increased intracellular calcium ion concentration also leads to the release of neuropeptides such as substance P and the stimulation of arachidonic acid production (Dray 1995).

Another mechanism by which peripheral sensitization can occur is the inhibition of the hyperpolarization that occurs after impulse generation. This slow after-hyperpolarization limits the number of action potentials that can be generated following stimulation. Prostaglandins and bradykinin act to inhibit this phenomenon allowing the neuron to fire repetitively (Dray 1995). This may also be one of the mechanisms activated by serotonin (Dray 1996).

Sensitization following the release of cytokines and leukotrienes appears to occur via indirect mechanisms whereby these agents stimulate other cells to release sensitizing agents. For example, leukotriene B4 stimulates the release of 8R, 15dihETE from leucocytes and this then acts to sensitize polymodal nociceptors (Levine et al. 1993). Some of these agents may also act to induce receptors for other inflammatory mediators (Rang & Urban 1995).

There is increasing evidence for the role of nerve growth factor (NGF) as a mediator of hyperalgesia (Anand 1995). Its actions include stimulating the release of neuropeptides and regulating other proteins such as proton activated ion channels (Anand 1995; Dray 1995; 1996). The induced hyperalgesia may be reduced by the administration of anti-NGF antibodies (Wooff et al. 1994).

It is now well established that in many tissues there is a significant population of nociceptors that remain essentially inactive under normal conditions. These sleeping or silent nociceptors are activated as a result of tissue injury with consequent release of chemical mediators and increased tissue hypoxia (Schmidt 1996). Schmidt estimates that they may represent approximately one-third of the total nociceptor population in joints (Schmidt 1996). They appear to be present in skin, joints and visceral tissue, however their presence in muscle tissue has yet to be demonstrated (Mense 1996). Once activated, these neurons exhibit marked sensitization with increased spontaneous discharge rates, reduced thresholds for evoked discharge and increased discharge rates in response to stimulation.

The processes of peripheral sensitization are clearly one way in which nociceptive system activity can be upregulated in response to tissue injury. It is apparent that the sensitization process is relatively complex and that different forms of sensitization may develop depending on the nature of the injury or disease. Recruitment of previously inactive nociceptors, spontaneous discharge, reduced activation thresholds and increased discharge rates in response to suprathreshold stimulation contribute to both spatial and
temporal summation of nociceptive input within the CNS. Ultimately, increased impulse activity in nociceptive neurons may be interpreted as pain at higher levels within the CNS. It is apparent, however, that there is not an invariable link between the degree of tissue damage and the level of pain experienced. Consequently, there must be other processes which contribute to upregulation of the nociceptive system and which can substantially modify the influence of changes occurring in the peripheral component of the nociceptive system.

**CENTRAL SENSITIZATION**

The process of central sensitization (Woolf 1994) is another important aspect of neuroplasticity that contributes to upregulation of the nociceptive system in response to injury. This process may provide a link between the presence of pain and sensorimotor and autonomic dysfunction in patients with musculoskeletal disorders. Central sensitization describes the changes occurring at a cellular level to support the process of neuronal plasticity that occurs in nociceptive system neurons in spinal cord and in supraspinal centres, as a result of activation of the nociceptive system (Woolf 1994).

This process is initiated by activity in peripheral nociceptors, particularly those associated with unmyelinated afferent neurons but it appears that the process can also be sustained in the absence of peripheral nociceptor input (Woolf 1983; Codere & Melzack 1987). Excitatory amino acid (EAA) receptors, particularly those of the N-methyl-D-aspartate (NMDA) subtype, have been strongly implicated in the generation of central sensitization (Woolf 1994; Dickenson 1995; Mao et al. 1995). Release of EAAs such as glutamate and concomitant release of excitatory neuropeptides such as substance P and neurokinin A from the presynaptic terminals of nociceptive afferents initiates a cascade of changes in postsynaptic spinal cord neurons (Duggan et al. 1988; 1990; Wilcox 1991). These include G protein mediated activation of phospholipase C leading to the release of Ca++ from intracellular compartments as well as the production of diacyl glycerol, activating protein kinase C, which in turn modulates ion channel activity (Woolf 1994; Mao et al. 1995). These changes upregulate NMDA receptors and enhance the neuron’s responsiveness to subsequent EAA release (Woolf 1994). One outcome of this upregulation of NMDA receptors is an increased Ca++ influx into the cell. Increased intracellular Ca++ concentration reduces transmembrane potential, activities NMDA receptor ion channels and renders the cell more excitable. One other effect of increased intracellular Ca++ concentration is to trigger the production of nitric oxide which is thought to be capable of diffusing out of the cell to bring about increased activation of the primary afferent neuron (Meller & Gebhart 1993).

While in recent years there has been a very strong emphasis on the role of the NMDA receptor in the central sensitization process, it has now become apparent that activation of the NMDA receptor may not be critical to the development of all forms of central sensitization. It has been suggested that the NMDA receptor is particularly important in relation to thermal sensitization and that it may not play a major role in mechanical sensitization (Meller et al. 1996). Coactivation of spinal z-amino-3-hydroxyl-5-methyl-isoxazolepropionic acid (AMPA) and metabotropic glutamate receptors induces an acute mechanical sensitization (Meller et al. 1996). This is mediated through activation of phospholipase A2 leading to the production of arachidonic acid. It appears to be the products of the cyclooxygenase pathway for metabolism of arachidonic acid that are of most importance in generating mechanical sensitization (Meller et al. 1996). Activation of NMDA receptors, phospholipase C, protein kinase C, or the production of nitric oxide do not appear to be important factors in the production of mechanical sensitization (Meller et al. 1996).

It is apparent, therefore, that the process of central sensitization is a relatively complex one and that in common with peripheral processes, the nature of molecular changes underlying central sensitization may vary depending on the nature of the inducing stimulus. In both cases it is becoming increasingly apparent that distinctions can be made between the processing of mechanical and thermal nociceptive information. Central sensitization contributes to a number of aspects of neuroplasticity including increased excitability of wide-dynamic range cells (Woolf 1989), increased receptive field size (Cook et al. 1987) and changes in somatic withdrawal reflexes (Woolf 1984). The development of tenderness (Tunks et al. 1988), the spread of pain from a primary location (Simons & Travell 1983), increased guarding of an affected area and alterations in skin temperature (Diakow 1988) are amongst some of the clinical characteristics which may be manifestations of neuroplasticity due to central sensitization.

The major consequences of these molecular changes in spinal cord neurons are increased synaptic efficacy and increased neuronal excitability. Neuronal plasticity leading to increased synaptic efficacy and increased neuronal excitability in spinal cord neurons conveying nociceptive information is also likely to influence activity in other neuronal pools with which the central nociceptive neurons make synaptic connections. This could account for changes in motor and autonomic nervous system function, which are clinical features of most musculoskeletal pain states.
MOTOR DYSFUNCTION

It is clear that this hyperactive state of spinal cord neurons is associated with important changes in terms of sensorimotor function. Woolf has shown that the establishment of central sensitization is associated with facilitation of flexor withdrawal reflex responses (Woolf 1984). A prolonged increase in the response duration is maintained for several days and in some cases may still be present weeks later, when tissue healing is presumed to have occurred (Woolf 1984).

In addition to increased muscle activation attributable to the influence of pain and tissue damage on alpha motor neuron function, it has been suggested that pain may influence the excitability of gamma motor neurons contributing to the development of increased muscle tension or spasm. The vicious cycle model is often alluded to in the literature. As outlined by Johansson and Sojka (1991), the basic concept is that stimulation of nociceptive afferents from muscles excites dynamic and static fusimotor neurons enhancing the sensitivity of primary and secondary muscle spindle afferents. Increased activity of the primary muscle spindle afferents increases muscle stiffness. This increased muscle stiffness then leads to increased metabolite production and following the vicious cycle formula, a further increase in muscle stiffness. In addition, increased activity in the secondary spindle afferents projects back onto the gamma system perpetuating the enhanced muscle stiffness. These effects are thought to be important in generating muscle spasm and pain (Johansson & Sojka 1991).

There are several studies by Johansson's group demonstrating enhanced activity in primary and secondary spindle afferents following the application of chemical mediators such as potassium chloride, lactic acid, bradykinin and serotonin (Johansson et al. 1993; Djupsjobacka et al. 1995). In addition to altered responses following local muscle injection, these researchers have also demonstrated modulation of secondary muscle spindle afferents following injection of bradykinin into the contralateral muscle (Djupsjobacka et al. 1995). This model may provide some explanation of muscle spasm when it is a significant component of the clinical presentation. However, it provides very little explanation of situations in which we see muscle inhibition and wastage as a result of pain and a number of studies have failed to show an increase in resting EMG activity as might be postulated by this model. Lund et al. (1991) refute the vicious cycle model and suggest that pain reduces the ability to contract muscles rather than making them hyperactive. Their model is strongly linked to the phenomenon of central sensitization. They propose that the effect of noxious stimulation is to alter the activity of type II spinal cord interneurons, such that there is increased inhibition of agonist motor units and increased facilitation of antagonist motor units. This leads to an overall limitation of movement in any desired direction. The proposed alterations in neural function would be manifest as a reduction in the ability to activate the agonist muscle, a time delay in activating the agonist muscle and a reduction in the maximum force output from the agonist muscle. Increased activity in antagonist muscles and a delay in producing reciprocal inhibition of these muscles might also be anticipated. Movement becomes slower, muscles appear to be weaker and the overall range of movement accomplished may be reduced (Lund et al. 1991).

Deficits of this type have been demonstrated in patients with low back pain and in normal subjects following the injection of hypertonic saline into the lumbar paraspinal muscles (Arendt-Nielsen et al. 1996) and the muscles of mastication (Svensson et al. 1996). It appears that this model may represent a good explanation of the limitation of movement that occurs in the acute pain situation. It is apparent, however, that motor dysfunction in chronic pain states may be a somewhat more complex phenomenon.

SYMPATHETIC DYSFUNCTION

Peripheral and central sensitization have also been implicated in changes in the autonomic function that are a feature of many pain states. Several authors have recognized that a link may exist between the experience of pain and alterations of sympathetic function and suggest that sympathetic outflow may influence or maintain afferent activity in nociceptive neurons (Roberts 1986; Campbell et al. 1992; Janig & Koltzenburg 1992; Devor 1995). The potential role of the SNS and postganglionic noradrenergic neurons in complex regional pain syndromes remains controversial, and little consideration has been given to the role of such mechanisms in less severe musculoskeletal disorders. Nevertheless, alterations in SNS function have been noted and abnormalities of somatosympathetic reflex responses have been demonstrated in patients with musculoskeletal disorders (Mani et al. 1989; Thomas et al. 1992; Smith et al. 1994).

Under normal physiological conditions, there appears to be no communication between sympathetic postganglionic neurons and afferent neurons (Janig & Koltzenburg 1992). Afferent neurons are not sensitized or excited by activity in sympathetic efferents or the release of noradrenaline (Shea & Perl 1985). Under pathophysiological conditions, however, increased alpha-adrenergic sensitivity in injured nociceptors has been demonstrated experimentally (Sato & Perl 1991; Devor 1995; Janig et al. 1996).
In sympathetically maintained pain states, Roberts (1986) proposed that central sensitization is maintained by ongoing activity of mechanoreceptors that are excited by sympathetic efferents. He hypothesized that a vicious cycle is established in which central sensitization maintains increased efferent sympathetic activity that in turn maintains peripheral mechanoreceptor sensitization. Alternatively, it has been proposed that low-grade activity of nociceptors may be necessary to maintain chronic central sensitization (Treede et al. 1992). Several mechanisms may account for an interaction between sympathetic efferents and mechanoreceptor afferents in the case of peripheral nerve injury (Devor 1995; Janig et al. 1996; Sato & Kumazawa 1996). These include coupling between sympathetic fibres and afferent terminals in a neuroma, coupling between unlesioned postganglionic and afferent terminals following partial nerve lesion and coupling following collateral spreading in dorsal root ganglia following peripheral nerve lesion (Janig et al. 1996).

It is clear, however, that the process of peripheral sensitization is essential for the expression of noradrenergic sensitivity in the case of tissue injury or inflammation (Janig et al. 1996; Sato & Kumazawa 1996). A form of indirect hyperalgesia, mediated by sympathetic postganglionic noradrenergic neurons has been proposed and is referred to as sympathetic–dependent or maintained hyperalgesia (Levine et al. 1992). It appears that noradrenaline acts to stimulate prostaglandin release, which in turn induces nociceptor sensitization (Janig et al. 1996; Sato & Kumazawa 1996). An important aspect of this model is that it does not require any increase in SNS efferent activity but rather implies increased sensitivity to the normal release of noradrenaline.

It is apparent that activation and upregulation of the nociceptive system induces changes in somatomotor and somatosympathetic function. The nature of these changes may be somewhat more complex than originally envisaged. There is still a good deal of research required to bring about a comprehensive understanding of the linkages between these systems.

CENTRAL INTEGRATION OF NOCICEPTIVE INPUT

Pain and nociceptive inputs can exert a strong influence on motor function, autonomic function and emotional state. As well as interactions at spinal cord level integration of nociception and other CNS functions must occur at higher centres. It is also clear that pain perception can be strongly modulated by descending systems originating in various parts of the brain and that the nociceptive system is normally in a state of tonic inhibition (Stamford 1995; Cervero & Laird 1996). This modulation can take the form of upregulation of pain perception as well as down regulation of pain perception associated with analgesic effects (Cervero & Laird 1996). It is now becoming apparent that, as well as being influenced by pain motor activity, autonomic functions and emotional state can in turn influence pain perception. As a consequence, the CNS is better viewed as an integrated cyclical system rather than the simple cause and effect system enshrined in the distinction between afferent and efferent aspects of function.

In recent years, functional imaging studies have provided abundant evidence of the distributed nature of the nociceptive system and the potential for close association between areas of the nervous system responding to pain and areas controlling autonomic and motor function and emotional state (Porro & Cavazzuti 1996). For example, it is clear that both the basal ganglia and the periaqueductal gray (PAG) region receive nociceptive inputs as well as coordinating important aspects of movement and motor control (Lovick 1991; Chudler & Dong 1995). Those regions of the brain encompassing the limbic system and areas such as the PAG also provide a neuroanatomical substrate for interactions between nociception, emotional state and autonomic activity (Lovick 1991; Chapman 1996). There is a considerable overlap between the neuroanatomical and neurotransmitter systems modulating pain perception and those controlling emotional state (Chapman 1996). Other papers in this issue deal with the importance of psychosocial factors in relation to pain perception and pain behaviour. Functional brain imaging studies are increasingly providing a means of bridging the gap between psychological studies and basic neurophysiological studies and allowing us to gain some basic understanding of the way in which nociception is intimately integrated with many other aspects of CNS function.

CONCLUSION

Recent advances in our knowledge of pain have provided a much greater insight into the many ways in which nociceptive system activity can be upregulated in response to tissue injury. It is clear that both peripheral and central mechanisms are important and the subtle variations in the mechanisms activated can result in different forms of altered sensitivity being induced. Rapidly developing areas of research are also improving our knowledge of the interrelationship between pain, motor and autonomic function and emotional state. We are beginning to move away from a largely peripheralist view of tissue injury to a much more integrated understanding of the influence of pain and injury on the central nervous system and the patient as a whole. Ultimately this should lead to the development of a more comprehensive approach.
References


Chudler EH, Dong WK 1995 The role of the basal ganglia in nociception and pain. Pain 64: 3–38

Coderre TJ, Melzack R 1987 Cutaneous hyperalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. Brain Research 404: 95–106


Devor M 1995 Peripheral and central mechanisms of sympathetic related pain. The Pain Clinic 8: 5–14


IAW 1986 Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the subcommittee on Taxonomy, Pain, Suppl 3


Lewis T 1936 Experiments relating to cutaneous hyperalgesia and its spread through somatic nerves. Clinical Science 2: 373–421


Meller ST, Gebhart GF 1993 Nitric Oxide (NO) and nociception in the spinal cord. Pain 52: 127–134


Woolf CJ 1984 Long term alteration in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. Pain 18: 325–343
Woolf CJ 1989 Recent advances in the pathophysiology of acute pain. British Journal of Anaesthetics 63: 139–146