3

Complex regional pain syndrome: Part 2

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Introduction

Complex regional pain syndrome (CRPS) is a widely diagnosed yet poorly understood condition. It affects people of all ages and straddles all the major specialties of medicine (Janig 1996). The aetiology and pathology of CRPS remains unclear. There is continued debate over the precise role of the sympathetic nervous system in the generation and maintenance of the condition.

Most recent literature supports claims that CRPS is a pain state, a neurological disease, and an immune disorder. The major focus at the present time is on specific changes within the neuro-immune system at the cellular/molecular level. Older literature tends to suggest orthopaedic origins (Schwartzman & McLelland 1987). Despite a massive amount of research, the condition remains enigmatic and one that is very much open to confusion. Hopefully, the leading role that the International Association for the Study of Pain (IASP) has played in its attempts to clarify the situation will be beneficial for a more rounded understanding that is so needed (Stanton Hicks et al 1995, Janig 1996, this work is discussed Chapter 2). Even so, most work in this area remains tautologous and reductionist in its perspective.

Before the adoption of the 'CRPS' designation a great many different diagnostic labels were used that many clinicians will be familiar with. Box 3.1 lists some of the disorders that are traditionally associated with sympathetic dysfunction but which are now grouped under the umbrella term CRPS (see Chapter 2).

Box 3.1 CRPS synonyms in the literature

- Reflex sympathetic dystrophy
- Algodystrophy
- Disuse dystrophy
- Sudeck's atrophy
- Post traumatic dystrophy
- Traumatic vasospasm
- Shoulder-hand syndrome
- Peripheral acute troponeurosis

Recall from the previous chapter that the distinction between CRPS Type I and CRPS Type II is based on the precipitating event: CRPS Type I follows tissue trauma, CRPS Type II follows nerve injury and represents what was formerly described as 'Sudeck's atrophy.'

The term 'reflex sympathetic dystrophy' (RSD)

It is now the accepted convention to refer to the condition known as reflex sympathetic dystrophy (RSD) as complex regional pain syndrome Type I (CRPS-I). The current IASP definition is reproduced in Table 2.1 in the previous chapter.

Renaming from the old term was prompted by the confusion that it produced. Stanton Hicks et al (1995) stated that the term Reflex Sympathetic Dystrophy was used so indiscriminately and that it was no longer clear as to what it meant. These authors highlighted that the changes seen in the condition 'may or may not be the consequence of a reflex' and that there was a growing amount of evidence reporting no alteration in sympathetic nervous system output/reflexogenic discharge in individuals suffering this condition (Campbell et al 1992, Roberts 1986). They also felt that correct management should prevent the condition becoming dystrophic. The consensus from Stanton Hicks et al (1995) was that most of the dystrophic changes seen in this type of patient were probably due to pain related disuse rather than pathological processes.

More recently the new definition (see Chapter 2) has been criticised and it appears that the diagnosis of this condition is still fraught with difficulties (Galer et al 1998). A cynical (*clinical*) view might be that valuable time is wasted by trying to reach a consensus on what CRPS-I really is and not spent on the management of patients! The view proposed here is that a better understanding of the known, or hypothesised, underlying mechanisms will ultimately facilitate better management strategies and more broad based, multifactorial thinking.

Models for reasoning

In the early 1990s Wilfred Janig (Janig 1990, 1992), a leading authority on CRPS and the biology of the sympathetic nervous system, suggested that a new paradigm was needed to better understand the condition. He stated that any model that warranted widespread acceptance would have to have the ability to include changes within not only the sensory and sympathetic systems but also the motor and neuroendocrine systems.

In the first volume of this series Louis Gifford wrote four chapters that overviewed the known mechanisms of pain as well as reviewing some of the limitations of mechanistic ways of thinking (Gifford 1998, 1998a,b,c). He made a call for a more integrative approach to the understanding of all pain problems (Gifford 1998). In order to do this he proposed the use of his Mature Organism Model (MOM) as an educational tool to help both patients and clinicians adopt a far broader perspective than the current biomedical and pathologically based ways of thinking and reasoning pain.

This account reviews the literature in an attempt to identify and bring together many current thoughts on the CRPS conditions. The aim is to consider the 'disease' or syndrome within a wider context. In order to do this the material available has been integrated into the framework of the Mature Organism Model (MOM) (Gifford 1998). Whilst not aimed specifically at CRPS, this model may have the sort of broad validity required by Janig (1990, 1992).

The MOM offers an operative paradigm describing the continuous and dynamic biological processes and interactions involved in sustaining life. There are three main elements involved: first, those concerned with the sensory systems or what Gifford terms 'sampling' or 'input' systems; secondly, those systems concerned with the processing, 'scrutinising' or assessing of gathered information—for example the central nervous system; and thirdly, those systems concerned with action, 'output' or 'responding', hence motor/behavioural, sympathetic/autonomic, neuroendocrine and neuroimmune systems. The model places a shared and balanced emphasis on the physiological, psychological and behavioural aspects and their dynamic integration. Hence, body affects mind, mind analyses and affects body; body affects CNS, CNS analyses and affects body; environment affects CNS and mind; CNS and mind influence body and environment, and so on. Like the biopsychosocial model, the MOM approaches injury, disease and pain as multidimensional and multilevel phenomena that can impact all levels. Thus all pain, whether acute or chronic impacts all components of the model—the sampling, the scrutinising, and the output, and as such all have the potential to become impaired or dysfunctional in some way. It is as fair to consider the impact of impaired or dysfunctional physiological activity in damaged tissues and nociceptors as it is to consider along side this impaired or unhelpful beliefs, attributes and behaviours in an individual with a pain complaint (see Chapters 6 and 8). The reader is advised to consult the original material (Gifford 1998, 1998a,b,c).

CRPS mechanisms relating to 'sampling' systems

The MOM proposes that the peripheral sensory nervous system continually 'samples' its target tissues/environment and may then report on its findings to the CNS. Thus, quickly, via impulses or more slowly, via axoplasmic transport systems, sensory fibres can relay information on the health and condition of the structures they innervate to the CNS for scrutiny. It is also worth noting that many sensory fibres, notably C fibres, are known to have a trophic role and relationship with their target tissues (see Chapter 2). Thus C fibres and the silent afferents too (see below) not only sample, but also scrutinise and respond to changes in their target tissues at this cellular level. Hence, nociceptors that detect damage or pathology in the tissues they supply may provide a direct 'local' frontline response in the form of peptide release as well as informing the CNS for its 'opinion' regarding possible action.

Key sensory fibres involved in tissue sampling are nociceptors—the Aδ and C 'afferent' fibres. Their role in the production/maintenance of symptoms in CRPS has been the focus of numerous research papers. Much work relates to changes in sensitivity when their axons have been injured, are degenerate, or have been severed.

Nerve damage, nerve irritation and neuropathic changes

Damage to peripheral nerves and their neurons causes a series of well documented changes (Devor & Seltzer 1999). Following injury the afferent fibres acquire novel and abnormal properties resulting in an altered, usually increased, afferent barrage to the central nervous system. This leads, in turn, to an alteration in the normal functioning of neurons found in the spinal cord including those in the intermediolateral horn, i.e. sympathetic preganglionic neurons. This is the basis for many of the proposed models of CRPS (see among others Bennett & Roberts 1996, Blumberg 1992, Janig 1996, Koltzenberg 1996, McMahon 1991).

Most of the literature focuses on the findings from animal models of nerve injury. A major finding of these intentionally produced nerve lesion studies is that the small Aδ and C fibres are reduced significantly in number both within the dorsal root ganglion and the dorsal horn (Lisney 1992, Bennett & Roberts 1996). This results in the loss of incoming electrical and trophic signals, which are thought essential to the maintenance of normal CNS functioning (Woolf 1992). The nervous system may respond to this 'loss' of input by massively increasing its sensitivity, a situation that has been termed 'denervation supersensitivity' (discussed in Chapter 2.)

Note that there are two mechanisms here which can cause the CNS to upregulate its processing sensitivity or 'gain'—one in response to increased afferent barrage from damaged neurones that have become electrically hyperexcitable, and one in response to a loss of normal inputs due to the death and hence loss, of sensory fibres.

It is found that damaged sensory neurones that fail to fully regenerate and reach their original targets (Lisney 1992, Woolf 1992) may continue to

show hyperexcitability, perhaps indefinitely. Clearly this will have a 'knock on' effect on both the scrutinising and output activities of the nervous system. In this way, nerve injury sets up the potential for ongoing increased sensitivity of dorsal horn neurons as well as many other cells and pathways throughout the CNS (McMahon 1992, Woolf 1992).

What is clear, is that damage to peripheral nerves can have quite far reaching repercussions on the processing and output pathways of the CNS. This poses problems for 'conventional' targeted approaches and pain treatments. The more research reveals about pain mechanisms the more traditional approaches are being forced to consider multiple sources, factors and mechanisms in many pain conditions. Thus, biomedically, a focus on a single peripheral source of pain may be inadequate in CRPS or for that matter any injury that causes pain, particularly the longer it has been established.

In addition to the above changes, many damaged sensory fibres demonstrate spontaneous activity in the form of ectopic impulse discharges (see Devor & Seltzer 1999 for an in depth discussion of the processes underlying these phenomena.) This is a well known peripheral mechanism that is thought to account for the spontaneous pains unrelated to any movement or other stimulus often reported by patients with neuropathic pains.

Spontaneous activity from injured nerve fibre axons is likely to result in pain or symptoms in the tissue areas that the affected nerves normally innervate. Thus, ectopic impulses generated from nociceptive nerve fibres that normally innervate the calf muscle will be 'felt' as pain in that muscle. The warning for the clinician is that nerve fibre hyperexcitability can result in pains in tissues that may be relatively normal. What is abnormal is the activity of their sensory supply.

The processes outlined here appears to present a perfect model for the initiation of neural changes that could lead to the development of CRPS. However, it is important for the reader to appreciate that the above findings are the results of direct nerve damage in animal models. There is some evidence to suggest that these injuries do not resemble those that are sustained by individuals who develop CRPS (Lisney 1992). This point has received a lot of attention in the literature. There is however a consensus that *careful* extrapolation from animal models of underlying mechanisms for individual symptoms is acceptable (Bennett & Roberts 1996, Janig 1996, Koltzenberg 1996).

Generally, the clinical picture of CRPS has been used by many as a reliable indicator of neural damage. Particular attention has focused on the presence of hyperalgesia to mechanical stimuli. Drummond et al (1996) biopsied skin from areas of hyperalgesia in subjects with established CRPS in an attempt to identify peripheral neural pathology. They compared these skin samples with those taken from areas of normal sensation in the same subjects. They found an increased number of 'nerve tangles' in the hyperalgesic region compared with the control areas but the differences did not reach statistical significance.

These rather weak findings for peripheral nerve abnormality appear to support the view of Lisney (1992) who concluded that hyperalgesia in CRPS is not likely to be as a result of direct changes in afferent fibres. He suggested a more central origin for these symptoms.

New experimental animal models have been developed that cause minimal direct axonal damage but rather promote an immune/inflammatory reaction in peripheral nerve trunks (Eliav et al 1999, Maves et al 1993). These models may prove to be more applicable to the study of the mechanisms relevant to CRPS Type I.

Electrical coupling

Undamaged normal afferent and efferent neurones show functional independence from adjacent fibres, that is, they are not stimulated by or cause the stimulation of their neighbours. Following nerve damage this situation can be altered with adjacent neurones demonstrating 'crossed excitation' (Devor & Seltzer 1999). Under such circumstances the firing of one neuron leads to the depolarisation of adjacent neurones to which it has newly made inappropriate contacts. Thus one explanation why normal movements might cause significant pain might be that mechanoreceptor or proprioceptor barrages mediated by Aβ nerve fibres with normal movement would be able to excite adjacent nociceptors that have acquired cross excitation capability. The normal and innocuous sensory signals effectively migrate into the pathways that process pain.

The nature of these contacts has been the source of widespread discussion in the literature. Early attention focused on the presence of false 'electrical' synapses known as ephapses (Doupe et al 1944, Granit & Skogland 1945). Lisney (1992) commented that these false synapses are only found in nerve end neuromas, but others have found them in regenerating nerves distal to the site of injury and in patches of demyelination (see, Devor & Seltzer 1999). However, so far, there is little evidence for this type of structural change in CRPS patients or the animal models that are used to reflect CRPS symptomology. Devor (1991) and McMahon (1991) have reported a scarcity of false synapses in animal models and have identified that when present, the coupling is between sensory fibres and does not involve the sympathetic fibres. Their presence in humans is unproven at the present time. However, there is a growing body of evidence to suggest that chemical coupling of sensory and efferent sympathetic fibres does exist (Devor 1991 & 1994, Koltzenberg 1996, Lisney 1992, McMahon 1991, Michaelis 2000).

Chemical coupling

Wall and Gutnik (1974, 1974a) were the first to demonstrate that damaged nerve fibres showed an increased sensitivity to adrenaline and noreadrenaline. Many developments of this early work have now appeared in the literature (Devor 1991, 1994, 1996, 1999; McMahon 1991, Michaelis 2000).

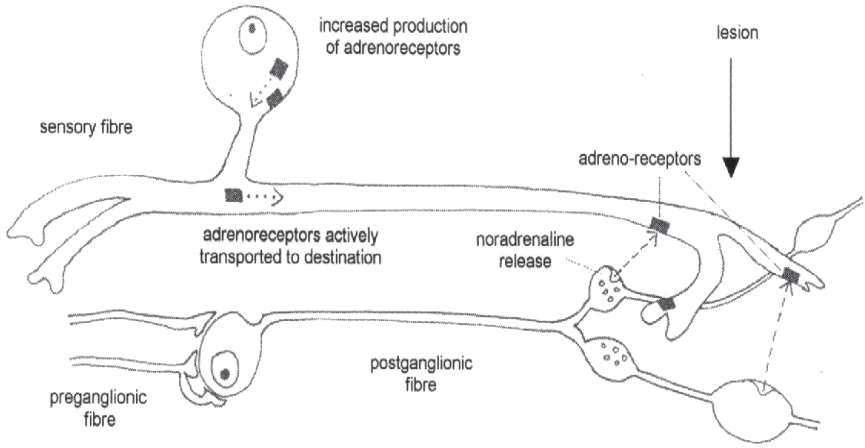

Fig. 3.1 The effect of nerve injury on adrenaline sensitivity. A nerve injury or lesion leads to an increase in adrenosensitivity. This is due to increased production and activation of adrenoreceptors.

Adapted from: Janig W, McLachlan, EM 1994 The role of modifications in noradrenergic peripheral pathways after nerve lesions in the generation of pain. In: Fields HL, Libeskind JC (eds) Pharmacological Approaches to the Treatment of Chronic Pain: new concepts and critical issues. Progress in Pain Research and Management Vol. 1. IASP Press, Seattle

It is important to note that damaged afferent nerve fibres show increased receptor expression for catecholamines, in particular, alpha-1 and alpha-2 adrenoreceptors (Devor 1996) (see Fig. 3.1). Thus, damaged sensory fibres change plastically by up-regulating (producing more) adrenoreceptors and activating refactory (dormant) adrenoreceptors. The result is an increase in the presence of active adrenoreceptors in the sensory fibre. No matter where the nerve is lesioned the adrenoreceptor increase may be far reaching. Active adrenoreceptors have been found on the cell bodies, axons, axon terminals, re-growing sprouts of damaged nerve fibres, and in nerve sprouts in neuromas. The end result is that the fibres become more sensitive to adrenaline and noradrenaline (see Coderre et al 1989). Devor (1996) stated that the aetiology of SMP in CRPS effectively boils down to adrenosensitivity on the sensory side as opposed to excessive output of adrenaline or noradrenaline on the (sympathetic) efferent side.

However, in CRPS Type I, there is no apparent or detectable nerve injury, which raises the question of how significant adrenosensitivity might arise here. Interestingly, there is modest evidence (discussed further later) to show that sensitised nerve endings in inflamed tissue can also become adrenosensitive (Levine et al 1986, Sato et al 1993, Drummond 1995). An important point is that there may not have to be a nerve injury for the development of adrenaline/noradrenaline chemosensitivity. Still, the vast

majority of research demonstrates the requirement of at least a partial nerve injury to produce anything like a reasonable adrenosensitivity (see Michaelis 2000 and discussion in Chapter 4.)

Injured sensory nerve fibres that have developed spontaneous ectopic activity have been shown to become more sensitive to both neuronally released and circulating catecholamines (Devor & Seltzer 1999, Janig & Baron 2001). It seems that even normal levels of noradrenaline and/or adrenaline release can activate damaged neurons and there is no prerequisite for any increase in sympathetic efferent activity (Habler et al 1987). This consistent message from the literature devoted to pain related to sympathetic activity repeatedly underlines that the abnormality at this state of our knowledge appears to lie with the sensory system and not the sympathetic system (see also Chapter 4).

This is a vital point as many therapies and procedures target the sympathetic system in attempt to reduce its activity and thus influence the disorder. There is potential for a reasoning error if therapies are based on shaky evidence. Although there is little doubt that methods that decrease the amount of noradrenaline in the circulation and/or tissue (e.g. relaxation) can benefit the individual, the consensus of biomedical opinion (Janig 1996, Michaelis 2000) is against interventions that aim to inhibit the postganglionic fibres directly in order to alter sympathetic output, e.g. interferential currents.

The increased expression of alpha adrenoreceptors on the cell membranes of damaged afferent terminals and re-growing axons has already been discussed. Coderre et al (1989) demonstrated similar increases of adrenoreceptors in the cell membranes of dorsal horn and dorsal root ganglion (DRG) cells of rats. This increase followed significant afferent barrage activity from a neuroma following nerve injury. This is another example of neuroplastic change in this condition, and supports the concept that the pathology that underpins CRPS need not reside in the periphery where symptoms are felt.

Coderre et al (1989) concluded that the presence of such receptors, wherever they occur on sensory afferents, offer a ready answer as to how efferent sympathetic activity can cause firing of damaged afferents. It is important to reiterate that the receptors are sensitive to adrenaline and noradrenaline regardless of its source of origin. Therefore circulating adrenaline released into the blood stream (e.g. result of psychological stress) could, possibly, cause an increase in nociceptive barrage and hence pain.

This is important information for the clinician as many CRPS patients complain of increased pain during periods of emotional stress. For example tension generated by physiotherapy appointments could exacerbate pain, especially if there have been previous negative experiences.

McMahon (1991) has also proposed an indirect coupling of the sympathetics with the afferents. This involves the autoexcitation of the sympathetic efferents, with the subsequent release of prostaglandins, a known inflammatory and pain producing agent (this concept is discussed in further detail below).

Silent afferents

In addition to increased impulse discharge from 'normally active' nociceptors there appears to be a novel afferent barrage produced by a sub group of nociceptors that have received increasing attention in the literature. These sub-types are known to remain silent even when extreme physical or physiological conditions occur. Thus, even when stimulated at levels that are known to cause normal nociceptors to discharge they fail to fire. It is for this reason they are often referred to as 'silent' or 'sleeping' afferents/nociceptors. It seems that they come into their own in the aftermath of tissue injury during the early inflammatory stages. In these conditions, probably stimulated by inflammatory agents, they 'awaken' and display increased excitability. (For a detailed account of the behaviour of these fibres see McMahon & Koltzenburg 1990, 1990a.) There is evidence that input from these silent afferents has a greater impact on CNS processing and sensitivity changes than that derived from activity in 'normal' nociceptors (Wall, personal communication). This may be significant in the development of CRPS and other chronic pain syndromes.

Is there a nerve injury in CRPS Type I?

The bulk of the discussion so far, on CRPS and SMP, is based on findings from animal models of neural damage and a subsequent increase in adrenosensitivity. As outlined in the previous chapter, the IASP definition of CRPS Type I requires that no history of relevant nerve injury has occurred, which makes the research discussed seem irrelevant to this condition. The definition also states that the diagnosis of CRPS is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. Problems arise here as better investigative screening and work-ups find lesions that would otherwise be missed—and hence challenge the classification of the disorder. For example it may be possible that many conditions designated CRPS Type I do in fact have nerve impairments or dysfunctions that are relevant, or could even be reclassified as neuropathies when scrutinised more closely. Thimineur and Saberski (1996) discuss this difficulty. They report three case studies of patients who were diagnosed as suffering CRPS Type I but were subsequently found to have nerve entrapments. Two of these individuals were reported to have a total resolution of symptoms following decompression of the entrapped nerve. Although impressive, no longer term follow ups were reported by these authors.

Thimineur and Saberski (1996) discuss the validity of the IASP definition of CRPS in light of their findings and suggest that oversights may occur if one accepts a diagnosis too readily. As anywhere, carefree labelling in patients exhibiting what in many cases are normal sequelae to injury, could lead to the patient receiving inappropriate (often protracted) management strategies. More detailed screening of patients may reveal alternative explanations for the patient's clinical presentation, and sometimes, the potential for more

appropriate management. We must be aware that the overzealous diagnosis of RSD/CRPS has received criticism in the literature (Janig 1992).

CRPS mechanisms relating to the 'scrutinising' systems of the CNS

We now know, from the work of Wall, McMahon, Woolf and others, that pain generating mechanisms that have become established in the periphery can have significant impact on the processing mechanisms within the central nervous system.

The clinical presentation of CRPS has led to the implication of the CNS both in the production and maintenance of symptoms (McMahon 1992, Janig 1992,1993, Blumberg 1992). For example, clinicians frequently encounter patients demonstrating extreme, prolonged, and maladaptive hypersensitivity states. The mechanisms underlying the conditions of hyperalgesia and allodynia are known to involve CNS changes (McMahon 1992, Woolf 1992). Also, the extensive and regional nature of the symptoms strongly suggests CNS involvement. Changes within the CNS are thought to be implicated where pain spreads to affect an entire region following an isolated lesion. Current knowledge suggests that the best explanation for this remarkable phenomenon relates to the maladaptive expansion of dorsal horn cell receptive fields (see Woolf 1992).

Louis Gifford outlined the role of the central nervous system in the production and maintenance of pain in the first volume of this series (Gifford 1998b). Similar changes are thought to occur in CRPS patients. The two main processes known to operate under such circumstances are 'wind-up' and 'sensitisation.'

Central changes in sensitivity and excitability within the dorsal horn are known to result from ongoing afferent impulse barrages derived from sensory neurones that supply or come from the site of injury. The afferent barrage reaches the second order target neurons in the dorsal horn[1] and sets in motion a series of electro-chemical reactions that alters their excitability. Several processes are thought to occur in parallel (see Fig. 3.2A, B and C).

1. The electrical impulse discharge that arrives at the afferent fibre terminals causes the release of an excitatory amino acid neurotransmitter called glutamate (Fig. 3.2A). Glutamate crosses the synapse to the second order neurone where it acts on a specialised AMPA receptor. If enough glutamate is released it effectively causes, via the AMPA receptors, the depolarisation of the dorsal horn neurons with a subsequent influx of both calcium and sodium ions into the neurone. Glutamate release thus increases the excitability of the second order neurone.
2. Further/continuous afferent barrage also causes the release of another neurotransmitter, substance P, from the afferent sensory fibres (Fig. 3.2B). Substance P then crosses the synaptic cleft and acts on available 'neurokinin' receptors on the second order neurones. This results in a further influx of calcium and sodium ions into the second neurone as

well as stimulating the release of calcium from stores within the cell. Calcium ions are known to be key 'messengers' responsible for increased responsiveness and excitability of the second neuron. The result is that the cell becomes 'charged', raising its excitability and sensitivity still further (Woolf 1992, 1994).

3. If the discharge of the primary afferent continues the intracellular sodium and calcium ion concentrations of the second neurone reach a critical level which leads to the activation of a previously blocked receptor type, the NMDA, or N methyl D aspartate receptor (Fig. 3.2C). The activation of the NMDA receptor involves the removal of a bound magnesium ion within it. This is caused by a change in its configuration triggered by the intracellular increase in calcium noted above.
4. Following the removal of the magnesium ion the NMDA receptor can be activated by further/on-going release of glutamate. Like the AMPA receptor, this activated NMDA receptor causes the cell to increase its potential flow of ions, and hence its electrical reactivity. In this way the cell up-regulates its firing capability. Now the second cell not only has a population of AMPA receptors available, but is also joined by activated NMDA receptors on which the glutamate can act. The result of this effective 'increase' in receptors is an increase in the cells ability to respond and fire to arriving glutamate. The cell firing becomes amplified in both amplitude and duration. These electrochemical changes form the basis of both wind-up and sensitisation. (For an in depth account see Doubell et al 1999, Coderre et al 1993, McMahon et al 1993, Woolf & Thompson 1991.)

Wind-up is a relatively short lasting process that requires an ongoing afferent impulse volley into the cord. *Sensitisation* is a long lasting process thought to be synonymous with the process of long term potentiation (LTP). LTP is a process widely studied in the hippocampus of the brain in respect to memory and learning and which is known to have the ability to persist for extended periods of time (Coderre et al 1993; Rose 1992).

Later sequelae that may result from the impact of nociceptive activity on the dorsal horn include:

- The formation of novel synapses—for example, Aβ fibres that normally terminate and synapse in lamina III/IV and V of the dorsal horn may sprout and form synapses in the outer laminae where nociception is processed. Thus normal, innocuous, proprioceptive and sensory inputs from normal tissues may, via this novel route, enter the nociceptive system and be processed in terms of pain (see Doubell et al 1999).
- The death of inhibitory interneurones in the dorsal horn, so called amino acid 'excitotoxicity' (Dubner & Ruda 1992). Here, high levels of excitatory amino acid neurotransmitters (i.e. glutamate) may actually lead to cell death. It seems that inhibitory interneurones are most vulnerable here. The clinical impact is that the system has lost some of its normal control mechanisms over nociception. This type of knowledge helps give a far better explanation for pain that takes many hours to calm down or that builds up very easily and quickly.

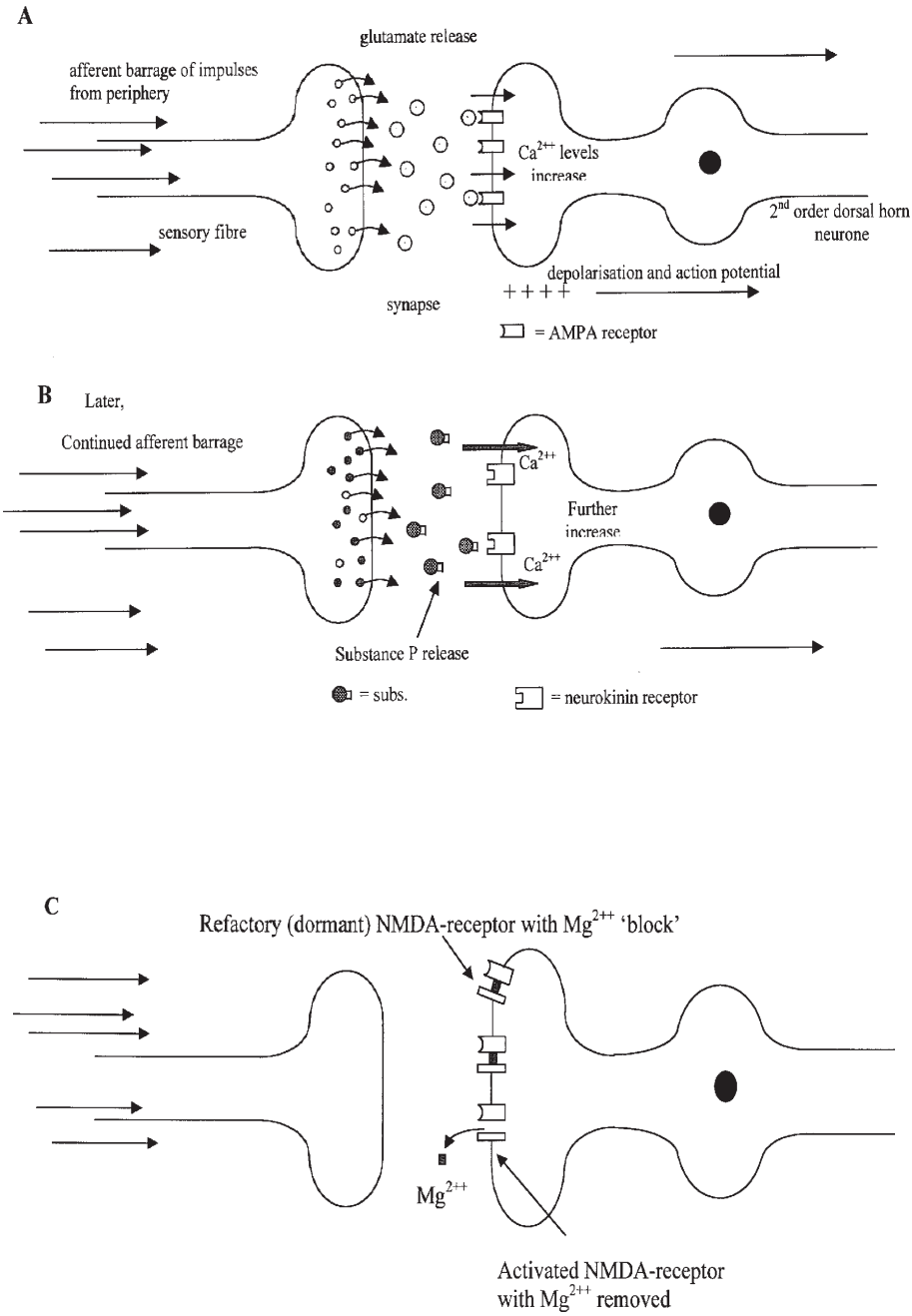

Fig. 3.2A, B, & C Some of the known synaptic events that occur in setting up sensitivity changes in the spinal cord dorsal horn.

Wind-up

Clinically, wind-up refers to the gradually increasing pain response that occurs when a given stimulus is repeated. For example, a CRPS patient may feel pain in the leg with ankle movement and with every repetition of the same movement the pain builds and builds to excruciating levels in a seemingly uncontrolled way.

Wind-up requires ongoing input into the system. This may be provided not only by repetitive stimuli, but also by the spontaneous generation of ongoing impulses from injury sites on peripheral nerve fibre axons as reviewed earlier, or even from relatively minor tissue injury sites. Whatever its origins, the ongoing input causes central changes similar to those described in the last section.

It seems that as the repetitive input is delivered to the CNS so the second order cells become more and more excitable and hence fire more and more easily. In animal models at least, if this afferent impulse activity is stopped or blocked the increased excitability generated in the secondary neurone diminishes and will rapidly return to a normal level. In a few patients it has been found that immediate and lasting relief occurs in response to procedures that block the afferent barrage (Wall 1995).

If this 'wind-up' scenario is the case for the highly sensitised CRPS patients it is little wonder that their attempts to get moving or do exercises are so easily beaten back by massive and long lasting increases in pain.

Concomitant tissue changes, such as neurogenic inflammation, alterations in circulation, local hypoxia, tissue deconditioning, oedema and tissue disuse, could all lead to an increase in peripheral sensitivity and afferent barrage further reinforcing the setting up and maintenance of central changes. This all suggests that our management strategies should carefully balance attempts to attend to and calm sources of ongoing input into the system with prevention of deconditioning. This means establishing progressive and paced early functioning. The emphasis here is on 'early' so as to avoid, as far as possible, the potential for maladaptive central changes becoming established. The cognitive-behavioural and self management approaches for the more established CRPS pain condition described by Suzanne Brook in Chapters 6 & 7 are important, as they allow time for gradual change and acceptance by the nervous system as well as the individual who is attached to it.

Sensitisation

Sensitisation differs from wind-up in that, once initiated, ongoing activity of the central neurons may continue *even in the absence of further afferent input*. Coderre et al (1993) describe two ways in which sensitisation may be initiated: the first is by continued low frequency input into the system: it can also be from a short lasting high intensity afferent burst into the CNS, a so-called 'neural scream' (Coderre et al 1993). This is of interest in the study of CRPS as the condition is often reported to have arisen from injuries that produce a short lasting but highly intense burst of nociceptive input. This certainly

occurs when an intact nerve is cut during animal experimentation (Devor & Selzer 1999).

Clinically, established sensitivity is a major hurdle and may be significant reason why many ongoing problems just do not respond to pain relief therapies satisfactorily. This is probably the single most important reason to persuade us to move towards management models that embrace pain management and improved function as outlined here by Brook (Chapters 6 & 7) and in many chapters in the other Topical Issues in Pain volumes of this series.

Mind-body link to the impact of wind-up and central sensitisation

Since there are known descending excitatory and inhibitory pathways from brain to spinal cord dorsal horn (reviewed in Fields & Basbaum 1999), it seems plausible that changes in mental state, like feelings of wellbeing, mood, expectation, learning and attention may impact the injury related afferent barrage effect on the central plasticity state. It is certainly known that activity of dorsal horn nociceptive neurones can be modulated up or down depending on the context in which painful stimuli occur. Changing the focus of attention towards the stimuli that produce pain, or to the pain itself, will increase the responsiveness, and changing it away reduces it (reviewed in Petrovic & Ingvar 2002). Prolonged focus of attention on pain often occurs in patients who have significant levels of pain or who are highly concerned about it or cannot for whatever reason make sense of it. Continued interest in pain, via central facilitatory pathways and mechanisms, will surely reinforce the electrochemical effects on the central cells leading to long term sensitivity changes and even to the potential for central pain generation (see Gifford 1998b). Fields and Basbaum (1999) do raise the possibility that pain could even *originate* from the CNS given enough central facilitation of dorsal horn neurones associated with nociception. See also the opening chapter by Melzack in this volume.

With this type of understanding it can be seen that even relatively minor degrees of nociceptive activity in the presence of significant cognitive or affective turmoil could have a more profound effect than if conditions were more evenly balanced. Also, it seems quite feasible neuroplastically that according increased attention to a given sensation can actually cause it to create a larger neurological impact on the CNS than if it were given less credibility or ignored. After all, if you want to learn something you have to concentrate on it (Gifford 1998b). Implications for early management and prevention of chronic pain and its impact, are to provide effective reassurance as quickly as possible, provide effective pain relief, and for the individual to keep active and occupied. It seems that doing nothing for too long allows us to dwell on and hence better establish our symptoms. The combination of emotional turmoil, uncertainty and increased attention to symptoms may be significant factors worthy of respect and consideration.

Are we then at risk of complex and chronic pains developing from acute injuries or acute pain onsets that are accompanied by heightened stress or depression? There is some support for this reasoning in the literature.

Van Houdenhove et al (1992) proposed a biopsychosocial hypothesis for the etiopathognesis of reflex sympathetic dystrophy. They screened a group of patients suffering reflex sympathetic dystrophy for psychological disturbances. They found that at the time of the initiating injury the patients had experienced an 'existential loss,' either as a direct result of the injury or exacerbated by it. They proposed a model of how this loss could lead to ongoing psychological and physiological symptoms. This may be an important and unique piece of work. In particular, it attempts to assess the affect of injury in the context of both the tissues and the mind and it offers a hypothesis that the 'unfortunate' timing of an injury could lead to amplification of normal adaptive responses to a maladaptive level. It seems reasonable that an individual who is under pressure—be it psychological, physical or both—is in a state of 'vulnerability' or 'reduced capacity to cope', and therefore less able to deal psychologically, physically, and physiologically with any additional burdens that may occur.

The more positive side of the coin is that acute management strategies that help patients to reduce the impact of pain (intensity and emotional), and that put the pain in a less threatening context by reducing levels of anxiety and fear, could well prevent its central impact from becoming maladaptive and hence chronic. Even in the longer term pain sufferer these strategies may be helpful. If something can be deemed unimportant, less threatening, or of little consequence it usually gets ignored. If this can become established, then positive neuroplastic changes to processing pathways are likely to have occurred.

Higher centre dysfunction?

Janig (1992) suggested the potential for dysfunction in the limbic system and the brain stem in CRPS patients. Until recently this theory has remained largely untested.

Thimineur et al (1998) published the results of their clinical study of 145 patients with CRPS. They assessed CRPS patients, patients with other pain conditions, and normal patients, for signs of brain stem dysfunction, and found a high incidence of trigeminal hypoaesthesia and lower cranial nerve (nerves 11&12) dysfunction in the CRPS patients. This finding, along with high incidences of bilateral motor weaknesses, was used as supporting evidence for their hypothesis that a sub-population of CRPS patients have dysfunction of their brain stem. They concluded that nearly 50% of their CRPS group had abnormalities of spinothalamic, trigeminothalamic and corticospinal function, which they suggested may represent abnormal function of the medulla. In summary they state:

> The etiology of these abnormalities is unclear but may be associated with prior head and neck trauma or congenital anomalies. Dysfunction in specific areas of the CNS, and we suggest one of these may be the ventral

medulla, may predispose to syndromes of complex regional pain upon peripheral nociceptive input. Specific pathophysiology cannot be determined currently, but mechanisms may involve any number of homeostatic and antinociceptive functions of the brainstem.

Implications of central mechanisms for physiotherapists

An understanding of the maladaptive changes that can occur within the 'scrutinising' CNS is enlightening to both the therapist and the patient. It may, one day, promote an alteration in approach and a broadening of reasoning models as well as open new opportunities for research.

What is becoming increasingly evident is the complexity of the problem and that a search for a single treatable 'nugget' looks increasingly unlikely in conditions like CRPS. Perhaps, for the present time, a more useful stance requires us to:

1. Accept the condition as being highly complex, difficult and perhaps impossible, to provide a single cure for.
2. Be able to see that it is very amenable to skilled multidimensional management approaches (see Brook's chapters and Chapter 8) whose aim is to provide the patient with better coping strategies and improved function and fitness despite the pain. One hope is that considerate therapists will learn how to communicate fully the implications of long term maladaptive nervous system plasticity to the patient and will, themselves, make positive alterations in their prognosis and management as a result. This requires great care and is highly skilled. But…
3. A degree of hope should wisely be maintained. As mentioned already, the considerable potential that the nervous system has to change plastically and adapt in a positive direction, when given the opportunity, may represent the most constructive avenue of therapy and research. Thus…
4. See the patient with established CRPS as containing in large part maladaptive neuroplastic changes that may have the potential to be overridden via good management. This requires a change of strategy from invasive or single modality approaches that attempt to 'fix' a presumed pathology, to those aimed at all the dimensions of the problem, thereby encouraging adaptive restorative changes in the patient's biology, physiology and psychology. It is the opinion here that understanding a cure for complex chronic conditions like CRPS requires a long and intense investigation into natural processes of recovery, healing and change. What is required are new and adaptive plastic changes in response to established maladaptive ones. It would be a major step if biomedicine could shift its attention away from the established, negative, pathology-focused research paradigm to include a more positive one whereby natural recovery physiology is better understood. Once we understand these processes better, we may well start to understand how they can be more efficiently promoted and nurtured.

5. See it as not inevitable, even in those who may be predisposed to it, and therefore preventable with good *early* recognition and good early multidimensional based management whose prime role is to reassure and restore physical confidence as quickly as possible. This requires the early identification of barriers to poor outcome (see Main & Watson Chapter 8, and chapters in Part 1 of Topical Issues in Pain 2). Pain control and pain management are very much a part of early preventive approaches.

> Central pain mechanisms and central information processing mechanisms related to pain remain poorly understood by the general clinical community. Even so, for the first time in the history of medicine, an understanding of central mechanisms involved in pain offers a far better explanation for the frustrating myriad complex and recalcitrant symptoms and symptom behaviours that these patients suffer and have often been blamed for. As the clinical impact of this new knowledge comes to be better understood by the general medical community, patients and their pains are more likely to get a better hearing.

Methods for managing these types of problems are included in this series of volumes and others (for example, see: Wittink & Hoskins-Michel 1997, Harding 1998, Main & Spanswick 2000).

CRPS mechanisms relating to the 'output' systems of the CNS

The greatest focus in the study of the conditions that now fall into the CRPS classification has been the proposed idea that the sympathetic nervous system (SNS) is somehow functioning in an overactive manner. This widely held belief is now thought to be inaccurate (Dotson 1993, Ochoa et al 1993). Incredibly perhaps, it is now mooted by some that sympathetic efferent activity is, if anything, *decreased*, in so called sympathetically related pain states (Devor & Seltzer 1999, Wasner et al 1999)! As far as pain is concerned, the general consensus seems to be that the sympathetic system is not abnormal and is not discharging in an abnormal way. Any variation of sympathetic output that does occur in these patients is, as in anyone, down to the degree of ongoing physical and mental challenges of everyday life. One point to consider though is that the mechanistic scenario that starts a disorder may well be different from the situation that occurs when it is established and investigated. As argued in the previous chapter, there are instances when changes in sympathetic activity may have a role to play in the development of the syndrome.

It was outlined in the 'sampling' section above, that injured sensory fibres, or intact sensory fibres in nerves that have suffered partial nerve injuries, appear to increase their expression of adrenoreceptors in response to injury. Under these circumstances normal rates of sympathetic firing and subsequent

release of noradrenaline will cause excitation of afferents leading to pain. Here, the sympathetic nervous system is said to be 'coupled' to the sensory system. If one thinks in a unidimensional way (i.e. not considering other influencing factors), the more noradrenaline released, as in periods of physical or mental stress, the worse the symptoms should become—and the better they should become in periods of calm or low sympathetic activity.

These points deserve reiteration—release of *normal* physiological levels of noradrenaline (and also circulating adrenaline) will result in the initiation of nociceptive activity and hence possible symptoms, if a coupling mechanism is present. In this way it seems rather unfair for the sympathetic system to receive all the attention when, to the best of our knowledge, its behaviour and physiology are quite normal. To remove parts of it surgically, or to immobilise its activities chemically using sympathetic blocking agents, seems to condemn the innocent party unjustly.

This finding that noradrenaline will activate nociceptors that are noradrenaline sensitive and hence cause pain is the current pathophysiological basis thought responsible for the clinical phenomenon described as 'sympathetically maintained pain' (SMP) first proposed by Roberts (1986). He highlighted the requirement of a 'positive' response to a sympathetic block for the diagnosis of SMP. Also, out of this definition, the concept of sympathetically independent pain (SIP) for pain that often has all the hallmarks of being related to a typical 'sympathetic' syndrome but which fails to respond to blocks, evolved (see previous chapter.) Some of the weaknesses and problems associated with this method of diagnosis are discussed in the following chapter.

A major point here, whether the sympathetic nervous system is normal or not, is that there is a mechanism by which it can exacerbate pain in the periphery. This then is an 'output' mechanism of pain generation which has repercussions for therapists. In the first volume of this series, Gifford (1998c p. 84) urged clinicians to consider how their interactions, physical examinations, treatments and physical manipulations and exercises might impact the activity of the sympathetic system. Anything that represents a threat to homeostasis, or is perceived in any way as threatening, will stimulate a sympathetic response and therefore have the potential to aggravate symptoms. Although somewhat unidimensional and 'peripheral,' this model may provide one feasible explanation as to why therapy-related flare-up can occur. It should also make us more aware of important components of the therapeutic alliance (see Noon chapter in Volume 4 of this series), e.g. in providing a model of the problem for the patient that actively tries to decrease any perceived threat and puts the patient at ease.

Micro milieu of the tissues

So far, the focus of the discussion for peripheral mechanisms of pain in CRPS has emphasised the up-regulation of adrenosensitivity following some form of nerve injury. These models of explanation for CRPS and SMP

are therefore more relevant to CRPS Type II (causalgia) because the diagnosis requires the presence of a nerve injury. Since CRPS Type I relates to tissue injury, models based on nerve injury are not relevant to its pathogenesis.

Here, but see also the previous chapter's discussions relating to vascular changes, three research findings are discussed that may apply to peripheral input/output mechanisms relevant to CRPS Type I.

First, as mentioned earlier, there is some evidence that sensory nerve endings in inflamed skin may can become sensitised (i.e. cause hyperalgesia) and can discharge (i.e. cause pain) in response to the presence of noradrenaline (see Levine et al 1986, Hu & Zhu 1989, Sato et al 1993). The findings that support this are:

1. If noradrenaline is introduced into inflamed skin in anyone, it increases the level of hyperalgesia and can cause pain.
2. Adrenoreceptor blockers can decrease hyperalgesia.
3. Sympathectomy can partially prevent hyperalgesia occurring (but see below).
4. C fibre nociceptors with receptive fields in inflamed skin acquire an excitatory response to stimulation of the sympathetic chain or to close arterial noradrenaline injections.
5. In the absence of inflammation however, sympathetic outflow does not excite C fibre nociceptors; in fact, it may even suppress their response to brief noxious stimuli.
6. It seems likely from the above that nociceptor end terminals in the inflamed skin express adrenoreceptors, though direct proof is still missing (Michaelis 2000).

Secondly, it has been found that the process of nociceptor sensitisation following injury seems, in part, to require just the physical presence of sympathetic postganglionic terminals (Levine & Reichling 1999). This mechanism can be viewed as essentially 'passive' since there appears to be no need for impulses arriving from sympathetic pathways in the CNS. It is as if the sympathetic terminals act as a physical 'docking station' for some inflammatory chemical agents and that once they have docked in their specific 'receptors' on the terminal a chemical reaction follows that then produces and releases a secondary end product. Chemical agents known to rely on this 'docking' to produce their sensitising effects during inflammation include bradykinin, noradrenaline and nerve growth factor (NGF) (Levine & Reichling 1999). It is known that both bradykinin and noradrenaline interact in this way to produce prostaglandins.

The action of noradrenaline on the very structure that releases it may seem odd. Be aware though that many chemical agents appear to have this 'autocrine' or self-stimulation effect; that is, they act on the very structure from which they were created and released. Thus, impulses arrive down the sympathetic postganglionic neurone cause the release of noradrenaline, which may then dock onto adrenoreceptors on the terminal membrane and

cause a further chain of events leading to the release of another chemical agent, in this case prostaglandin I_2!

Thirdly, Gibbins (1992) has added to this discussion with the finding that about 20% of the sympathetic postganglionic fibres to peripheral blood vessels contain substance P which is discharged in response to tissue damage. It is widely accepted that peripherally released substance P is a potent pro-inflammatory mediator. Gibbins (1992) also demonstrated that substance P can cause a slow autocrine depolarisation of postganglionic sympathetic neurons with a possible subsequent release of the prostaglandin PGE2 (McMahon 1991). PGE2 is a well known pro-inflammatory compound.

The above findings support the notion that chemicals 'dumped' by the SNS into peripheral tissues may directly (noradrenaline to nociceptor coupling), or indirectly (stimulates inflammation formation) lead to an increased discharge of sensitised afferents and hence produce pain.

Other evidence to support this includes the finding that, during inflammation, plasma extravasation is reduced post sympathetomy (Janig 1992) and that there is a flow-independent increase in vascular permeability for macromolecules in RSD patients (van Oyen et al 1993)—a feature that indicates ongoing inflammation (see discussion in Chapter 2).

Although these arguments seem convincing, a few workers have demonstrated that the SNS may have an important role in actually inhibiting inflammation—a quite reasonable mechanism if one considers the importance of bringing healing to a halt in order to conserve energy during times of threat/stress. As an example here, Ochoa et al (1993) reported a *reduction* in the flare response following microstimulation of postganglionic efferents in an animal model.

There is modest evidence to suggest that the target tissues alter their responsiveness to sympathetic outflow following tissue damage. These changes may well be normal physiological responses to tissue injury and inflammation, and hence essential parts of the tissue repair processes. Bennett (1999) advises that pathology, i.e. CRPS Type I (SMP), be viewed as a result of normal physiological processes persisting abnormally after healing—hence persistent inflammation and persistent C fibre nociceptor noradrenaline sensitivity. Not only this, but to fit with the occasionally dramatic and massive early manifestation of CRPS Type I, it may also be sometimes worth thinking in terms of maladaptive or 'excessive' physiological responses from the very start.

The complex dynamics of the interaction between the sympathetic nervous system and inflammation and injury, the sensory system, the vascular system, the immune system and perhaps other systems involved in the control of local tissue responses is emerging, but still remains complex, contentious, occasionally contradictory and sometimes unclear.

Sympathetic sprouting

A recent area of interest for the understanding of mechanisms more relevant to CRPS Type II has been the demonstration of sprouting of sympathetic

efferents into the dorsal root ganglia following experimental neuronal injury in animal models (see Fig. 3.3a and b). These sympathetic 'sprouts' have been shown to form 'baskets' of nerve filaments that grow round and embrace dorsal root ganglion cell bodies (i.e. cell bodies of sensory cells) whose axons have been experimentally injured distally. The baskets are not present in normal 'non nerve injured' animals and appear to be triggered by the nerve injury. Several neurotrophins have been linked to this process including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) as well as a family of cytokines (GP–130, IL–6, and leukemia inhibitory factor (LIF), see Ramer et al 1999 for a detailed review.) What the research is starting to show is that this rather strange phenomenon may represent a physical and physicochemical site where the sympathetic nervous system can yet again 'couple' with the sensory system and hence cause symptoms via its activity. According to the review by Ramer et al (1999) the evidence supporting this is quite compelling even though there is still a long way to go. Janig (1999) however has suggested that to be functional these sprouts need to be capable of discharging at 10–15hz and his studies indicate that the sprouts are incapable of such discharge frequencies. Indeed, in an excellent recent review of the role of the sympathetic nervous system in neuropathic pain, Janig and Baron (2001) caution that there are only a very few studies which show that normal physiological activity of sympathetic nerves or normal physiological concentrations of noradrenaline, in animal models, can elicit impulses and hence pain in damaged primary afferent nerve fibres (see next chapter). It seems that most researchers pour on vast quantities of noradrenaline or hyperstimulate the SNS in order to test whether adrenosensitivity occurs! Having said that it has still been shown that normal nerves do not respond to the same large quantities/activities or concentrations.

Finally, from a clinical perspective this dorsal root ganglion 'coupling' site draws attention to a proximal pathophysiological location of a potential pain mechanism. It also further emphasises the difficulties of targeted mechanism based treatment.

Immune based disease?

There has been an increase in the amount of attention that the immune system has received in the pathogenesis of this condition (Thompson 2001, Calder et al 1998, van Oyen et al 1993, Weihe & Nohr 1992). Several cytokines are known to be involved in communication between the immune and nervous systems and include tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and leukemia inhibitory factor (LIF). There is little doubt that nervous tissue is not only sensitive to these chemicals but also uses them to determine its responses to injury. They may even be significant factors in governing whether the response is adaptive or maladaptive.

The nervous system is thought to be able to recruit the immune system by influencing specific cell types. The main cell that has been studied here is the macrophage. Macrophages form an important interface between the inflammatory response to injury and the recruitment of the immune system.

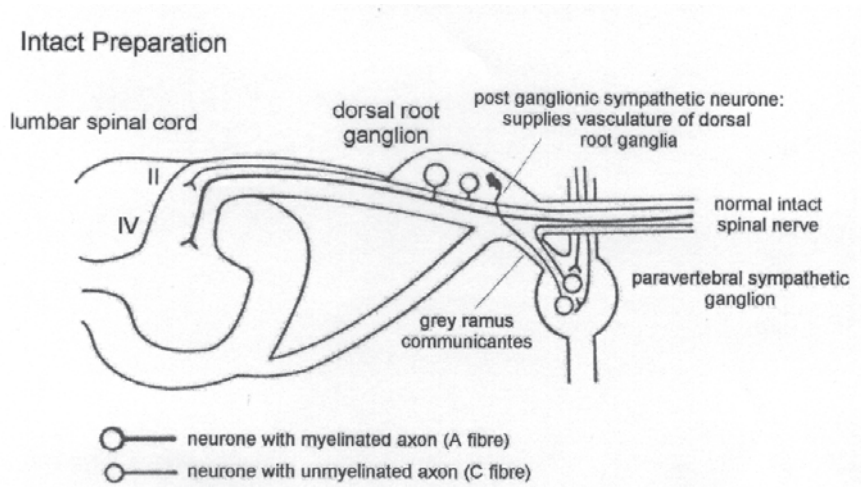

Fig. 3.3a Relation between afferent neurones and their projections in the lumbar outflow. Here, there is no interaction between the sympathetic post ganglionic fibres and the afferent fibres (A and C fibres).
Adapted from: Janig W, McLachlan EM 1994 The role of modifications in noradrenergic peripheral pathways after nerve lesions in the generation of pain. In: Fields HL, Libeskind JC (eds) Pharmacological Approaches to the Treatment of Chronic Pain: new concepts and critical issues. Progress in Pain Research and Management Vol. 1. IASP Press, Seattle

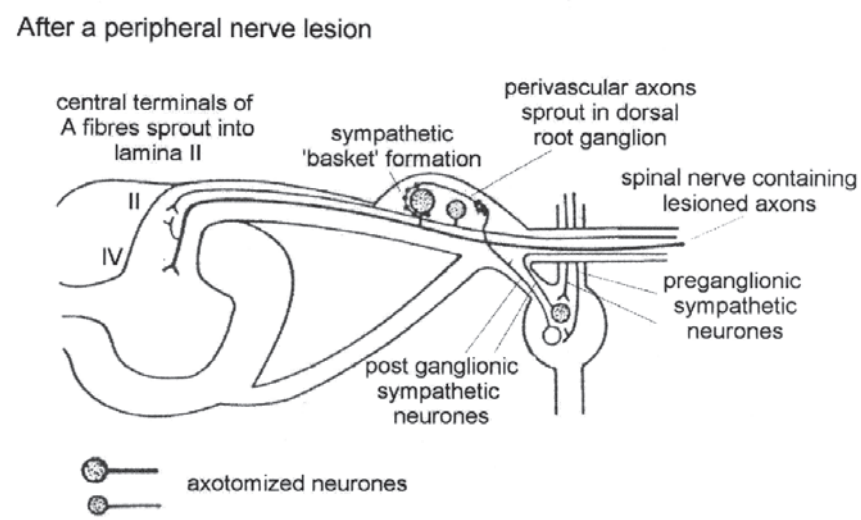

Fig. 3.3b After ligating and cutting the sciatic nerve postganglionic perivascular axons in the dorsal root ganglion area sprout to form basketlike structures around injured neurons cell bodies.
Adapted from: Janig W, McLachlan EM 1994 The role of modifications in noradrenergic peripheral pathways after nerve lesions in the generation of pain. In: Fields HL, Libeskind JC (eds) Pharmacological Approaches to the Treatment of Chronic Pain: new concepts and critical issues. Progress in Pain Research and Management Vol. 1. IASP Press, Seattle

For example, they are known to play an active role in the generation of pain following neuronal damage (Ramar et al 1999, Weihe & Nohr 1992) and they have been shown to have membrane receptors to several neurotransmitters (Weihe & Nohr 1992). This indicates that their activity may be modified in some part by the nervous system. These workers further postulate that other immune cells may have similar receptors.

Weihe and Nohr (1992) have suggested that there may be an interaction between individual neurons (both sensory and sympathetic) and macrophages, lymphocytes and mast cells that reside within the nerve i.e. intrafasicularly. This is an interesting observation as this type of interaction would be impossible to diagnose. These authors also comment that if such a process became established, it may 'spread' more proximally and could involve both the dorsal root ganglion and dorsal horn. They support this hypothesis with findings from biopsied sympathetic ganglia.

Calder et al (1998) have suggested that the sensory-immune interaction may occur in the target tissue. They took skin biopsies from symptomatic areas of patients diagnosed with CRPS Type I (RSD). They used a barrage of immunostaining tests in order to ascertain which cell types were present in the skin. An important point was that there was no macroscopic evidence of inflammation in the areas studied. However, they did find an abundance of Langerhan cells (cells known to be derived from mature macrophages) in their samples. Significantly, these cells are not present in normal skin or in that from patients with other types of neuropathic pain states (McAllistar et al 1996).

Langerhan cells are capable of producing several different types of cytokines including TNFα, IL-6 and also the neurotrophin nerve growth factor (NGF). All these compounds are capable of producing pain and changes within sensory neurons (Michaelis 2000).

Calder et al (1998) also suggest that these and related molecules may gain access to the central nervous system and cross the blood-brain barrier producing a more systemic effect and illness behaviours (see Watkins et al 1995 for an in-depth and fascinating account of these processes.)

Recent evidence supports the hypothesis that this condition is in part a neuro-immune disease and, quite likely, a psycho-neuro-immune one, too. This is a fascinating prospect that would go some way to explaining why a mulitifaceted approach to its' management appears to be successful. There is obviously much more work to be performed, but once again we are made aware of the need for paradigms that are inclusive of such concepts!

Conclusion

This chapter and the last have reviewed some of the significant recent research findings into the mechanisms thought responsible for CRPS. This chapter has placed the overview of mechanisms within the context of the 'sampling–scrutinising–responding' circle proposed in the Mature Organism Model (Gifford 1998), and as a result has considered potential points of interest at

the sensory nerve terminals, along the sensory nerve, within the central nervous system at all levels and finally focuses on the impact that some of the output systems may play.

- The idea that CRPS relates purely to sympathetic dysfunction or abnormality is challenged powerfully. Clinicians are urged to be cautious and to consider the problem as not having a specific pathological site to target.
- The notion that there is a useful medical cure for the problem has to be considered very carefully (see next two chapters). There are probably only a few real clinical experts in the world who have a good broad understanding of all the issues and are highly skilled at blocking procedures. As the reader will find out in the next chapter, many of the procedures that medicine has to offer are dramatic, invasive, not necessarily guaranteed, and based on unproven unidimensional models that usually target the SNS, which in all probability is quite normal. Referring patients on to inappropriate and possibly inexperienced specialists, and thus over-medicalising the disorder, needs to be considered very carefully with the present state of knowledge (see Chapter 4).
- The problem is more than just pain, swelling and stiffness; it invariably involves a very physically disabled and unhappy patient. Considering the multidimensional impact of the problem and all facets of it in relation to the patient's life should guide better management strategies.

ENDNOTE

1 Second order cells in the dorsal horn have many names and may be a source of confusion. They are also known as: transmission, or 'T' cells; wide dynamic range cells (WDR); nociceptive specific cells (NS); or simply, dorsal horn cells. Their cell bodies lie in the dorsal horn and their axons may then communicate with other nerve cells at many levels. This may be locally, segmentally, intersegmentally, or beyond up to the brain where further synapsing, scrutinising and processing occurs.

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