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# Tissue and input related mechanisms

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## Introduction to pain mechanisms

The standard way in which pain mechanisms are viewed is broadly linear in aspect. For example, an acutely twisted ankle or whiplashed neck involves tissue damage. The tissue damage creates inflammation which leads to the sensitisation of nerve endings in the damaged tissues. As a result of this ‘nociceptive’ pain mechanism, increased numbers of impulses are relayed into the CNS resulting in enhanced sensitivity to movements and mechanical forces with or without ongoing discomfort. This is linear in that it has a clear start (tissues) and a clear end (brain). The resultant thinking is: pain is the result of tissue mechanisms and nociception—therapy should therefore be focused on the tissues as well as at preventing excessive impulse activity being generated from the relevant nociceptors.

Appreciating that for every input to the CNS/brain there is likely to be some form of scrutinising and some form of response/output leads us from a linear mode of thinking to a circular ‘Mature Organism Model (MOM)’ mode. Not only that, the discussion in Chapter 2, whereby the brain samples itself and the ongoing events in the environment occurring at the same time as it receives information from the damaged tissues, should make us realise that an individual’s psychology (their thoughts and feelings) is brought into play in all injury related situations and painful experiences, whether acute or chronic. Linear descriptions of pain mechanisms may be preventing our thinking reaching beyond the sensory dimension of pain or into the biological mechanisms involved in outputs back to the tissues and environment. If we really think about it, there are two easily accessible therapeutic input points: via the tissues where it hurts, and via the brain where all the integrative processing of information goes on. One influences the other. Since a wealth of recent literature is indicating the far superior strength of psychosocial factors over physical factors in determining satisfactory outcome and functional recovery following the onset of a pain

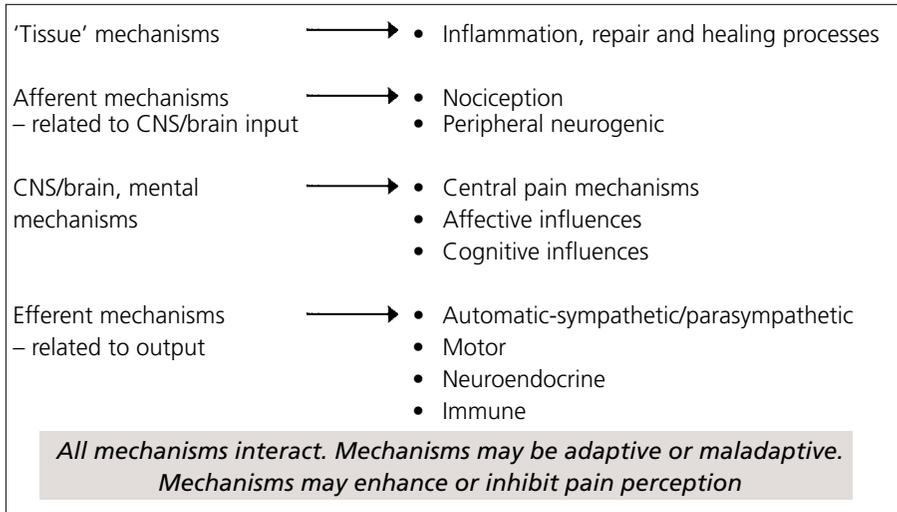
complaint (see Ch.15 and the Introductory Essay), it behoves us to think again as to how and where therapeutic inputs should be targeted. A balanced attitude is obviously necessary. What we have to accept is the fantastic sophistication of biology that should make us discard the notion that it is always going to be possible to fix a pain passively via the pure tissue or the 'bodily' effects of pills, surgery, manipulation, or any passive therapy. It is perhaps far wiser to be involved in helping to establish the best possible conditions for natural recovery (Wall 1989). This appears to involve a parallel and well balanced focus on restoration of best possible tissue health/return of function in parallel with a recognition of and focus on relevant cognitive and affective factors. These issues are explored in many of the chapters in this book.

Pain mechanisms have been usefully categorised into five separate classes for manual therapists (Butler 1994, Jones 1995, Gifford & Butler 1997). The current mechanisms in general use and their descriptions are detailed (for more detailed discussion see Gifford 1997, Gifford & Butler 1997).

- 1 **Nociceptive mechanisms.** Here pain is primarily derived from nociceptive activity in the target tissues of the nervous system. This can involve any musculoskeletal tissue that has a nociceptive innervation, for example: disc, bone, joint, ligament, tendon and muscle tissues. Nociceptive mechanisms may relate to mechanical forces, and/or to the chemical environment of the nociceptors, for example inflammation, ischaemia or the presence of catecholamines (adrenaline and noradrenaline). In the clinic, labelling a particular tissue as the 'source' of the pain is in effect stating that the pain mechanism is nociceptive.
- 2 **Peripheral neurogenic mechanisms.** This relates to pain generated from abnormal impulse generating sites in the axons and cell bodies of peripheral nerve fibres/neurons. Acute nerve root pain and carpal tunnel syndrome are examples of classic neuropathies that have a predominantly peripheral neurogenic pain mechanism. Injury to peripheral nerve tissue is highly likely in whiplash injury (see Ch. 1).
- 3 **Central mechanisms.** Following tissue injury, nociception and/or peripheral nerve injury, plastic changes in the CNS/brain result in alterations in processing of afferent information. For example, normal non-noxious movements and standard physical tests on undamaged tissues may provide inputs that get centrally processed in terms of pain. A second perspective is that the CNS/brain may spontaneously generate neural activity that results in pain—without necessarily any reference to peripheral inputs from the tissues. This central generation of pain can be viewed as a 'pain memory' (see Ch. 4).
- 4 **Sympathetic/motor mechanisms.** This category recognises that activity in the sympathetic and motor systems may enhance pain secondary to a peripheral sensitising process (e.g. nociceptive and peripheral neurogenic). There may be nothing wrong with these output systems for them to generate pain (see Ch. 5).
- 5 **Affective mechanisms.** This category accepts the potential of negative and unhelpful emotions and mood states to give rise to pain, or more likely, to

be an integral part of the pain problem with many potential repercussions (see Ch. 4)

In order to integrate these mechanisms into the MOM some additions and alterations in terminology need to be made (Fig. 3.1).



**Fig. 3.1** Pathobiological mechanisms related to pain perception and physical and mental/psychological dysfunction.

First, note that the term pathobiology is used in order to shift the focus from a rather compartmentalised pain mechanism thinking to a broader concept that analyses all mechanisms and processes from the perspective of the tissues, where injury begins, to then involve the sampling, processing/scrutinising, output systems in every clinical case every time.

Secondly, note that processing/scrutinising involves affective and cognitive processing and thus brings psychosocial factors into the clinical equation every time. Thus, tissue injury, as in the acute stages of whiplash (see Ch. 1), involves not only tissue damage and the activation of nociceptors, but also:

- the transmission of information to the CNS/brain;
- the multilevel scrutinising and processing of that information in parallel with personally relevant recalled information; and finally
- the production of a response appropriate to the individual—physiologically and behaviourally.

Even though tissue damage and subsequent nociceptor activity can be seen as a dominant mechanism in acute pain, the individual imposes unique affective and cognitively derived neurobiological influences onto the tissue derived processing activity and hence produces a unique output/response to it. All mechanisms are involved in every pain state, however, in some pain states a particular pain mechanism may dominate. Thus, pain arising from an acutely

inflamed joint may be ‘physiologically’ dominated by tissue and nociceptive mechanisms, whereas chronic pain associated with whiplash may be predominantly characterised by maladaptive central/processing mechanisms alongside maladaptive affective and cognitive features.

The rest of this chapter discusses tissue mechanisms and mechanisms relating to ‘input’ into the CNS/brain. Chapter 4 looks at CNS/brain/mental or ‘scrutinising’ mechanisms and Chapter 5 at mechanisms relating to output.

## **Tissue mechanisms**

A consideration of the types of tissues injured (see Ch. 1) and their healing capacity is vital. It is necessary to integrate knowledge of healing times of various tissues in parallel with the best conditions required for best recovery. This is a massive topic and one that requires greater scrutiny (see Butler & Gifford 1999). There are some basic facts that need to be fully acknowledged.

Tissue injury is traditionally divided into a 3 phase time-dependent process that leads to recovery. The phases are, inflammation, fibro-proliferation/repair, and remodelling. Further, there are three types of healing: healing by regeneration whereby lost and damaged tissues are replaced with tissue that has similar functional and morphological characteristics; healing by repair, where damaged and lost tissue is replaced by granulation tissue that eventually matures to form a scar; and healing by contraction. All three components probably play a role in all recovery processes, which one dominates depends on the tissue injured. Thus, removal of 70% of the liver elicits a healing reaction dominated by regeneration, and the outcome is a normal liver in a matter of days. Injury to the oesophagus may result in an exuberant proliferation of myofibroblasts, excessive wound contraction, and contracture. A wound on the anterior tibial surface, where the skin’s attachment to the periosteum prevents contraction, forces healing almost exclusively by repair, and a large scar results (Martinez-Hernandez & Amenta 1988).

An important message is that most injuries of the musculoskeletal system heal predominantly by repair (scarring), not by regeneration, and this means that these tissues are very unlikely to ever be the same again. This is a fundamental fact that is not at all well accepted—by medicine, by the allied health professionals who deal with rehabilitation, or the general public. The tendency is to believe that medicine has the tools to fix a given problem when the reality is far from this.

It can be argued that a degree of maintained sensitivity in previously damaged but repaired (scarred) tissues is of adaptive (protective) value since the tissues may be weaker or more vulnerable to further damage. Thus, a degree of end range sensitivity or modest discomfort in prolonged positions may well be an adaptive legacy that helps to prevent further injury to a weak and biomechanically compromised tissue. Having said that, the nervous system’s role in maintaining an adequate modest protective sensitivity appears to be very open to individual variation and not always easy to control. Two people who suffer exactly the same injury may have quite different long-term outcomes. It seems

that there is a homeostatic balancing act going on that can be easily unbalanced and if unbalanced long enough is very difficult to adequately reestablish in a more adaptive and functional way.

Chronic pain and excessive ongoing tissue sensitivity following whiplash are excellent examples of how homeostatic information processing mechanisms may overcompensate and be maintained in a maladaptive state. Thus, tissues may remain exquisitely sensitive and unnecessarily painful long after a reasonable healing time. The sensitivity state is out of all proportion to the likely state of the tissues or their needs. In fact, due more to lack of use than significant damage, it is likely that the excessive sensitivity helps maintain the tissue in a weaker state than they otherwise would be. Clinically it can be very helpful to direct patients attention away from a 'pain equals tissue damage' model towards one focusing on strengthening tissues that have had prolonged underuse. For this to occur the patient needs to be convinced that excessive sensitivity is a problem in its own right and that it is not necessarily an honest reflection of tissue damage.

It is conceivable that even healed but scarred tissues, once more extensible and strong, may send positive biological messages to the nervous system that enable a downshift in its sensitivity. If the nervous system is constantly sampling tissues that are weak, inextensible and little used it will logically tend to want to remain sensitised. By contrast, if the tissues become fitter, the system's overall need to remain sensitive and vigilant may be far less.

It is hoped that if readers can go along with this they will appreciate the need for changes in tissue health in parallel with changes in patient beliefs, attitudes and feelings towards their tissues and their pain (see Chs 11, 13, & 15).

The disc is a good example of a tissue that, once damaged, is unlikely to heal well. In fact the literature indicates that injured discs are prone to degenerate more rapidly than they otherwise would with the passage of time. For example, Osti et al (1990) investigated the effects of surgically producing a 5 mm long and 5 mm deep cut in the anterolateral aspect of young and otherwise normal lumbar discs of sheep. They lesioned 3 discs in each of 21 sheep. Overall the experiment revealed that the lesion lead to a progressive failure of the inner annulus which occurred between the 4th and 12th month in the majority of animals. As early as the first 1-2 months there was evidence of nuclear degeneration, nuclear displacement, the presence of clefts and the early loss of definition between the outer nucleus and inner annulus in several of the discs. These features were present in all discs examined at 12 months. Moderate narrowing of the disc space was observable in most discs by 8 months and was moderate or marked in all discs by 18 months. Osteophytes were apparent in some after 4 months and in all discs by 8 months. Marked changes over the whole length of the end-plates were also observed. Unhappily, what this is saying is that once a disc annulus is damaged the whole disc and its end-plates degenerates further and really quite rapidly.

Against this rather dismal prospect is the more hopeful and well known finding that many people with degenerate tissues and clear evidence of tissue pathology and abnormality are perfectly healthy and complain of little or no pain

(see Ch. 15). Far better to view injury-related ‘degeneration’ as an unfortunate but thoroughly adaptive process.

The use of carefully controlled loading at an optimal time during repair of injured ligaments and tendons has wide support since it undoubtedly promotes healing (for references see Buckwalter 1995, Buckwalter 1996). Tensile loading of damaged tendon tissues appears to cause the repair cells and matrix collagen fibrils to line up parallel to the axis of tension (Liu et al 1995). Lack of tension leaves the repair tissue cells and fibres disoriented. Loading may also alter the rate of tendon repair. For example, three weeks following injury, surgically repaired tendons treated with early mobilisation had twice the strength of repaired tendons treated with immobilisation (Gelberman et al 1982). This is a very useful piece of information that can be given to early whiplash patients to help them understand the need for early and progressive movement.

The following important information is taken directly from Goodship et al (1994):

The initial haphazard arrangement of collagen fibres is modified as functional loading is restored, resulting in a return toward parallel alignment of fibers. It has been suggested that immobilization of collagenous structures results in a decrease in mechanical strength that is never regained on remobilization. These facts would suggest that complete rest may be contraindicated except in the very early period after injury and controlled exercise should be introduced in a progressive manner from an early stage. Application of physical stimulation includes specific exercise regimes and the use of physiotherapy, particularly in the early stages, to provide low levels of loading and cause fluid dispersion.

A comment here is that passively moving a patients neck with grade II or III mobilisations for 2–3 minutes 3 times a week during a treatment session is likely to be wholly inadequate. Consider too that some passive techniques in some patients may involve a great deal of fear/anxiety/tension by the patient that may be a factor in actually exacerbating and maintaining the pain. Far better that the patients convincingly learn the underlying principles, and then apply regular movement themselves (see Ch. 7).

## **Input/sampling mechanisms**

The CNS/brain samples the state of damaged tissues primarily via the nociceptive system. Tissue damage alters the chemical environment of the nerve terminals of nociceptors and as a result sensitises them so that their firing capability becomes dramatically increased (Schaible & Grubb 1993, Levine & Taiwo 1994, Schmidt et al 1994). This equates to ongoing discomfort, due to the continued spontaneous firing of sensitised nociceptor populations, as well as to increased sensitivity to movement, touch/palpation and postures. Thus, gentle movements, gentle pressure on the tissues or sustained postures cause nociceptors to fire far more easily and for far longer than normal. Inputs that normally do not hurt or cause discomfort now easily hurt and cause pain to

continue for a while after their cessation (see Gifford 1997).

In addition to nociceptive input there is now much evidence to support the importance of tissue—CNS/brain communicating links via the immune and hormonal systems (De Souza 1993, Rivier 1993, Udelsman & Holbrook 1994, Watkins et al 1995, Pennisi 1997). Thus, damaged tissues, and immune cells in damaged tissues, release chemical messengers (e.g. cytokines and prostaglandins) that are sampled by the CNS at specific sites. These sites may be in areas of the brain which specifically sample the blood's contents, for example the tuber cinereum of the hypothalamus, the pineal gland, and the area postrema of the caudal fourth ventricle (Westmoreland et al 1994, Sternberg & Licinio 1995, Watkins et al 1995), or at specific peripheral nerve terminals in the periphery. For example, an important blood sampling route may be via visceral afferent neuron terminals in the liver (Pennisi 1997, Sternberg & Gold 1997). These then relay into the CNS via the vagal nerve (Watkins et al 1995). Since the liver screens the blood and lymph for toxins, pathogens and pro-inflammatory chemicals like cytokines, it is well disposed for processing and then relaying this information on to the brain for further scrutiny.

These sampling sites, in parallel with incoming nociceptor pathways are directly linked to major processing and output centres in the limbic brain that have been shown to be capable of strongly influencing our illness behaviour (Watkins et al 1995, Maier & Watkins 1996). Thus infection, tissue damage like whiplash perhaps, and other bodily threats are dealt with in ways that stubbornly dictate a required behavioural response with its associated mood states. Our psychological state may be quite firmly dictated by the state of our body. It is little wonder that following a severe and disturbing accident many people become withdrawn, passive, moody, angry, worried and frightened—for the biological determinants of these behaviours are well entrenched and are very difficult to over-ride. Of most concern here is understanding the merger from this adaptive early stage to its chronic maladaptive maintenance so often seen in many physiotherapy outpatient departments.

In whiplash actual damage may occur to the sampling pathways (see Ch. 1). Thus, injury to peripheral nerve tissues may result in abnormal or perverted function of the sensory nervous system conduits (Devor 1994, Gifford 1997). This proposal can be expanded to include the ascending sensory tracts in the cord and brainstem which may well be damaged in some whiplash injuries.

Since it is vital for survival that the CNS/brain maintains contact with its 'body' it is little wonder that quite potent homeostatic mechanisms come into play to try to restore contact and maintain the pathways. Thus, when peripheral nerve fibres are injured, related populations of cells in the spinal cord may dramatically enhance their sensitivity, expand their receptive fields, make new and often inappropriate connections, and become spontaneously active to try and compensate for the loss (Woolf et al 1992, Woolf 1994, Woolf & Doubell 1994). Similarly, the surviving proximal remains of severed neurones may up-regulate their sensitivity (Devor 1994). Unhappily, this may occur not just at the damaged zone but along the axon to include the cell body. Adjacent normal peripheral neurones may even upgrade their sensitivity, too (Devor 1994).

The message here is that damage to vital linking systems/sampling pathways can have devastating consequences when viewed at biological levels looking at maladaptive neural reactivity and plasticity. Thus, thinking in terms of 'peripheral' input mechanisms only, it seems that there is a far greater potential for a maladaptive response if the nervous system is injured than if the target tissues alone suffer injury.

Injury to peripheral nerve is known to take time to generate a response. For instance, A $\delta$  fibres that are injured may remain totally silent for the first day or two after injury, but then slowly increase their spontaneous activity over the following two weeks. C fibres tend to increase activity as the A fibres decrease theirs (Devor 1994). This may be several weeks after the original injury. Think of the unfortunate whiplash patient who for the first few days feels stiff and sore (nociceptive mechanism due to tissue damage likely), but some days or weeks later starts to develop weird symptoms in odd places (peripheral neurogenic mechanism with central mechanism repercussions). Not only is it strange and worrying to the patient it also gets seen as the first signs of malingering by many unenlightened health professionals. This type of knowledge is hugely useful in helping the patient understand the mechanisms of their pain as well as helping to validate their pain experience.

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