Chapter 21
Pathophysiology of Pain

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Key Learning Points

- Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- Physiological pain is related to impending tissue damage (nociceptive pain) or actual tissue damage (inflammatory pain); it has a physiological function in preventing damage and promoting protection and thereby enabling healing.
- Pathological pain is not related to tissue damage but is the result of disease or a lesion of the nervous system (neuropathic pain) or central sensitisation processes (nociplastic pain). It is not a symptom of peripheral disease or injury, but is a disease in its own right.
- Peripheral sensitisation is the result of increased nociceptor activation due the inflammatory response and typical for most nociceptive-inflammatory pain states.
- Central sensitisation is the result of processes in the spinal cord and brain and the result of an imbalance of increased excitatory and diminished inhibitory processes.
- Central sensitisation occurs in response to any nociceptive input, but usually resolves with healing. Persistent central sensitisation beyond the period of healing is the hallmark of many chronic pain states.

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21.1 Introduction

Pain is classically defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Currently there is an ongoing discussion on updating this definition, but consensus has not been reached [2].

The mechanism by which a damaging stimulus in the body is perceived as painful by the brain is a complex one. The complexity of the process results from the nervous system not being a 'hard wired' system, but exhibiting plasticity which enables it to modify its function under different conditions [3].

As per definition, pain serves the purpose of preventing tissue damage and protecting the body whilst it is healing. Under certain conditions, pain can become maladaptive and then persist as chronic pain. This pain serves no protective function and is described as pathological pain as opposed to physiological pain [4]. Applying these principles, nociceptive and inflammatory pain are physiological pain conditions, while neuropathic and CNS dysfunctional (now 'nociplastic') pain are pathological pain states [5]. The latter are then no longer a symptom of another disease, but diseases in their own right [6]. In order to adequately treat physiological, but even more so, pathological pain, an understanding of pain mechanisms is required.

21.2 Peripheral Mechanisms

21.2.1 Nociception/Transduction

Painful stimuli are detected by nociceptors, which are free nerve endings located in tissues and organs. They have high thresholds and, under normal circumstances, only respond to noxious stimuli [7].

There are two distinct types of nociceptor;

- High threshold mechanoreceptors which stimulate small myelinated Aδ-fibres and transmit a well-localised sharp or pricking sensation that lasts as long as the stimulus.
- Polymodal nociceptors that stimulate small unmyelinated slowly conducting C fibres. As well as responding to mechanical stimuli they are activated by thermal and chemical stimuli e.g.: hydrogen ions, potassium ions, bradykinin, serotonin, adenosine triphosphate and prostaglandins.

The ion channels for noxious stimuli have been partially identified; the transient receptor potential (TRP) family of these ion channels and here in particular the vanilloid-type TRP 1 (TRPV1) have been studied in most detail [8]. This receptor is sensitive to higher temperatures, acidity and capsaicin, an exogenous ligand (extract of chili pepper) and receptors like this one are currently being investigated as therapeutic targets for pain therapy.

Nerve growth factor (NGF) is also involved in the transduction process, as it binds to its receptor Tropomyosin receptor kinase A (TrKa) and thereby triggers increased transduction in pain states, in particular inflammatory pain. A monoclonal antibody against NGF, tanezumab, has shown very promising effects in current trials in osteoarthritis and chronic low back pain and is currently awaiting regulatory approval [9, 10].

21.2.2 Conduction

Voltage-gated sodium channels mediate conduction along primary sensory afferents. As for all other impulses throughout the body, action potential propagation is dependent on these channels. There are two types of sodium channels, differentiated by their sensitivity to tetrodotoxin. Both types are present in nociceptive neurons, with the tetrodotoxin-resistant type only present in nociceptors, which makes it a potential target for novel analgesics. Further research has identified three such voltage-gated sodium channels, (NaV1.7, NaV1.8 and NaV1.9), which seem to have specific roles in pain modulation [11, 12]. Mutations of these channels are linked to congenital insensitivity to pain and erythromelalgia [13], and attempts are currently being made to identify blockers or modulators of these channels as analgesics [14]. Research is also focusing on these sodium channels as a pharmacogenomic target [15].

Nociceptors also have voltage-gated calcium channels, which are found on the presynaptic membrane and are involved in neurotransmitter release at the dorsal horn. These are modulated by alpha-2-delta compounds such as gabapentin and pregabalin, now first-line treatments of neuropathic pain and central sensitisation [16].

Pain is transmitted by primary afferents, which have their cell bodies in the dorsal root ganglion (DRG). They terminate in the dorsal horn of the spinal cord. The dorsal horn cells are divided into specific regions or laminae called Rexed's laminae with I being the most superficial [17].

- Aδ-fibres are fast conducting and transmit the first sharp pain on initial stimulation. They terminate mainly in lamina I, but also send some fibres to lamina V of the dorsal horn where they synapse with second order neurones. They contain the neurotransmitter L-glutamate.
- C fibres are unmyelinated slow-conducting fibres which transmit a less well-localised persistent aching pain that lasts after the initial stimulus has gone. They terminate in lamina II of the dorsal horn. As well as glutamate, they contain several other neurotransmitters including neuropeptides, such as substance P, and calcitonin gene-related peptide (CGRP), cholecystokinin, brain derived neurotrophic factor and glial derived neurotrophic factor. C fibres express several presynaptic receptors that modulate transmitter release. These include cholecystokinin (CCK), opioid and gamma-aminobutyric acid subtype B (GABA B) receptors. Apart from the CCK receptor, they inhibit the release of transmitter.

- Aβ-fibres conduct low intensity mechanical stimuli which convey touch and not pain, however in chronic pain states they are involved in the transmission of pain (phenotypic switching) [18]. They terminate deeper in the dorsal horn in laminae III-VI

21.3 Spinal Cord Mechanisms

Primary sensory afferents terminate in the spinal cord where they synapse with cells of the dorsal horn. Nociceptive specific neurons are located mainly in laminae I and II but also lamina V and respond only to noxious inputs under normal conditions.

There are a number of different cells involved in the relay of painful stimuli including nociceptive specific cells and wide dynamic range neurons. Wide dynamic range neurons are located mainly in lamina V, but also in III and IV to a lesser extent, where they respond to stimuli from Aβ-, Aδ- and C-fibres [17].

The cells of the dorsal horn involved in nociception express a number of receptors;

- AMPA (a-amino-3 hydroxy-5-methylisoxazole) receptors which bind glutamate
- NMDA (N-methyl-D aspartate) receptors which also bind glutamate
- Neurokinin receptors NK-1 which bind substance P
- GABA-A receptors which are ligand-gated calcium channels that hyperpolarize the cell and reduce responsiveness to stimulation
- Voltage-gated calcium channels
- Glycine receptors that provide an inhibitory function

The ability to detect a potentially damaging noxious stimulus is mediated by glutamate acting on the AMPA receptor following stimulation of Aδ-fibres. The other receptors and neurotransmitters are involved in the modulation of the response.

When a high intensity noxious stimulus arrives at the dorsal horn via C-fibres, initially glutamate is released which acts via the AMPA receptor. As stimulus intensity increases, then other neurotransmitters are released such as Substance P. Slow post-synaptic currents are set up which are mediated by a number of receptors including the NMDA receptor. These are also involved in the modulation of the pain response [19].

21.3.1 Ascending Systems

Noxious information is conveyed from the dorsal horn to the brain via several ascending tracts in the spinal cord. The majority of the wide dynamic range neurons and nociceptive specific neurons are conveyed anterolaterally in three pathways [20]:

- The spinothalamic tract: Its fibres cross over to the contralateral side and pass through the brainstem to nuclei in the thalamus, finally terminating in the somatosensory cortex where pain is perceived and localised.
- The spinoreticular tract: It terminates in the reticular formation and has projections, which terminate in the pons, medulla and periaqueductal grey matter. It is involved in descending inhibition of pain.
- The spinomesencephalic tract: It is also involved in the modulation of descending control.

21.3.2 Descending Control

The dorsal horn receives inputs from higher centres that modulate the response to nociceptor input [21]. The descending control of output from the dorsal horn comes mainly from areas in the brainstem, namely the periaqueductal grey matter, the raphe nuclei and the locus coeruleus [22, 23]. Inhibitory tracts descend in the dorsolateral fasciculus and synapse in the dorsal horn. The key neurotransmitters involved are noradrenaline and serotonin. Noradrenaline acts via post synaptic α-2 receptors; the action of serotonin is less specific. Endogenous opioids are also involved in descending inhibition at a spinal and supraspinal level [22, 23]. These endorphins and enkephalins, acting via the descending system, are thought to be responsible for the analgesia induced by stress.

As well as descending control from the brainstem, nociceptive impulses are also attenuated by input via Aβ-fibres (transmitting information on touch), which is the basis for the use of Transcutaneous Electrical Nerve Stimulation (TENS) for analgesia, but also for simply rubbing a hurting body part. This observation formed the basis for the initial gate-control theory of pain [24].

21.4 Pain Modulation

The above description of pain explains the initial sensation of pain immediately following injury, however it does not explain the more complex phenomena associated with pathological pain due to neuroplasticity. These phenomena have a number of different causal mechanisms, which occur initially in the periphery, but later mainly in the dorsal horn as the main site modulation of painful stimuli.

21.4.1 Peripheral Sensitisation

Tissue injury results in release of inflammatory mediators, such as bradykinin, histamine, K+, H+, 5-Hydroxytryptamine (5-HT, also known as serotonin), ATP and nitric oxide, from damaged cells [25]. Breakdown of arachidonic acid by

cyclo-oxygenase produces leukotrienes and prostaglandins. Immune cell activation results in the release of further mediators including cytokines and growth factors. These mediators provide an 'inflammatory soup' which produces a painful area of primary hyperalgesia. These inflammatory mediators spread into the tissues surrounding the initial area of injury to produce an area of secondary hyperalgesia [26]. Therefore, most pain after injury of any kind is not purely nociceptive, but can be more correctly described as nociceptive-inflammatory.

The inflammatory mediators mentioned above act either by stimulating nociceptors themselves or by acting via inflammatory cells to stimulate release of additional pain-inducing agents. They also modify the response of primary afferents to subsequent stimuli, either by changing the sensitivity of the receptors, or by modulating the voltage-gated ion channels. For example, after tissue and nerve injury, N-type calcium channels become more active, resulting in greater release of glutamate in the spinal cord [27]. The magnitude of the current generated by sensory-neuron specific sodium channels is also increased.

Chronic inflammation and also nerve injury have an effect on the presence and distribution of voltage-gated sodium channels, which can become concentrated in areas of injury and produce ectopic discharges. Sensory neurone-specific sodium channels have a significant role in chronic pain states. Studies have shown them to become concentrated in neurones proximal to a site of nerve injury and this plays a role in hyperalgesia and allodynia (pain elicited by a normally non-noxious stimulus) [17]. In addition, NGF binding to TrKa receptors increases peripheral sensitivity as discussed before [28].

Not all sensory neurons are active all the time and this peripheral sensitisation will recruit "dormant" nociceptors, thus increasing the receptive fields of dorsal horn neurons and increasing the intensity and the area of pain [29].

21.4.2 Central Sensitisation in the Dorsal Horn

Central sensitisation is an increase in the excitability of the dorsal horn so that the dorsal horn cells have a lower threshold and respond to low intensity stimuli that are not usually painful. It also results in a greater response to supra-threshold stimuli thus producing the symptoms of allodynia and hyperalgesia. There are several mechanisms which occur at the dorsal horn and contribute to chronic pathological pain states by central sensitisation. These will be discussed in the context of neuropathic pain, as they are most relevant there.

21.5 Neuropathic Pain

Neuropathic pain is caused by disease or injury of the somatosensory nervous system and is related to a far-ranging number of aetiologies e.g., ischaemic, traumatic, infectious. Characteristics of neuropathic pain include spontaneous

stimulus-independent pain and pain that is stimulus-dependent and exhibits the features of allodynia and hyperalgesia. There are a variety of different mechanisms responsible for the generation of these symptoms, which may be quite different from patient to patient [30].

21.5.1 Mechanisms of Neuropathic Pain

The pathophysiology of neuropathic pain involves central and peripheral mechanisms and is in principle a '*maladaptive response of the nervous system to damage*' [31]. Usually more than one mechanism may be involved and producing a unifying hypothesis for all neuropathic pain states is inappropriate [32].

21.5.1.1 Peripheral Mechanisms

Spontaneous Ectopic Discharge

Normal primary afferent neurones require the input of a stimulus in order to reach firing potential. It has been shown that after a nerve injury spontaneous firing in the afferent neurone occurs. A and C fibres have been shown to demonstrate oscillatory activity resulting in ectopic firing [33]. Cross-excitation of other neurones increases this effect; in particular Aβ-fibres, usually not relevant for pain transmission, show ectopic discharge due to phenotypic switching [18].These phenomena are particularly relevant to the development of hyperalgesia, allodynia and chronic pain after nerve injuries.

Reorganisation of expression of ion channels in the peripheral nerves is responsible for these ectopic discharges [34]. Both sodium and calcium channels have been shown to be involved with their altered expression increasing the excitability of neurones. The afferent barrage provided by spontaneous discharge from neurones provides a constant input to the central nervous system that may induce central sensitisation [33].

Altered Gene Expression

Damaged peripheral sensory neurones undergo Wallerian degeneration and lose contact with peripheral targets and the supply of neurotrophic factors. The sensory neurones undergo altered gene expression, the result of which is a change in the type and level of neurotransmitters released in the spinal cord [35]. For example, some A-β fibres appear to release transmitters normally associated with nociceptors such as substance P. This seems to contribute to central sensitisation [36]. A change in gene expression also results in either up- or down-regulation of ion channels, in particular different types of sodium channels involved in ectopic spontaneous activity.

Spared Sensory Neurones

Changes have also been found in uninjured sensory fibres that are alongside those affected by a lesion. They frequently show the opposite gene expression changes from their damaged neighbours; possibly due to increased bioavailability of neurotrophic factors. This can result in increased activity in the spared afferents, although the exact mechanism is not understood [35].

Involvement of the Sympathetic Nervous System

Some patients exhibit neuropathic pain that is dependent on activity in the sympathetic nervous system. After a peripheral nerve injury, a coupling develops between the sympathetic nervous system and the sensory nervous system. Axons involved develop increased α-adrenoceptors and therefore have an exaggerated response to circulating catecholamines [37]. Morphological changes to the nerve follow with sympathetic axons sprouting into the dorsal root ganglion, forming baskets around the cell bodies of sensory neurones [38]. These changes lead to sympathetically maintained pain [39]. Evidence for a sympathetic component to a patient's pain include sympathetically maintained, often unilateral, limb pain, oedema, vasomotor and sudomotor asymmetries.

Effects of Bradykinin

This main plasma kinin, a vasodilator peptide, is involved in hyperalgesia associated with inflammatory pain, with a change in expression of its binding sites within the dorsal root ganglion after nerve injury [40]. Furthermore, there may be a role of the endogenous opioid dynorphin A as an agonist at the bradykinin receptor [41].

21.5.1.2 Central Mechanisms

The central mechanisms potentially involved in the generation of neuropathic pain are thought to result in neuroplastic changes in the CNS. A phenomenon termed central sensitisation occurs after peripheral nerve injury [42]. Central sensitisation changes the way the neurones respond to subsequent inputs [31]. This may result in spontaneous ongoing pain and abnormally evoked pain (allodynia and hyperalgesia) [29] .These mechanisms that are thought to be responsible occur primarily in the dorsal horn.

Wind-Up

The term wind-up describes the altered response of the dorsal horn neurones to repeated input from C-fibres [19, 29]. Following brief, repetitive C-fibre stimulation, the dorsal horn cells respond in a linear fashion. However if the stimulus continues, further C-fibre activation produces an amplified response in the dorsal horn to the same intensity of stimulus.

This phenomenon is mediated by the NMDA receptor [43]. Activation by sustained C fibre input leads to opening of the channel, an increased intracellular calcium concentration and an increased response to glutamate. Glutamate is the main excitatory neurotransmitter released from primary afferent neurones that acts at postsynaptic receptors. The NMDA receptor in its resting state is blocked by magnesium which is released when the cell is depolarised, thus opening the channel in the receptor and allowing an influx of sodium and calcium and further depolarisation. When a painful stimulus arrives at the dorsal horn, the cells are initially depolarised by glutamate acting at the AMPA receptor, thus allowing removal of the magnesium block. Once the stimulus is removed, the dorsal horn cells continue to fire for several seconds. There is potential for this to be modified pharmacologically; in particular NMDA antagonists such as ketamine prevent these phenomena including hyperalgesia [44]. Wind up is relatively short lived (seconds to minutes), whereas central sensitisation persists and thus the exact relationship remains unclear [45].

Central Sensitisation

Central sensitisation is also mediated by the NMDA receptor. Under conditions of prolonged C-fibre activation, depolarisation of the dorsal horn cells causes the NMDA receptor to lose its magnesium block [43]. Substance P, acting via its receptor, the neurokinin-1 receptor, prolongs this depolarisation and allows further influx of calcium. The increase of calcium in the dorsal horn activates calcium-dependent kinases such as protein kinases A and C, which are then able to phosphorylate amino acids within the NMDA receptor to produce a conformational change in the structure. This permanently removes the magnesium block in the receptor and allows it to be activated by glutamate. The process of central sensitisation differs from windup in that the changes remain long after the C-fibre input has ceased. Furthermore, the magnesium is removed by posttranslational changes in the NMDA receptor and is not just depolarisation induced [29, 36, 46].

Central Disinhibition

Central disinhibition results from loss of modulatory control mechanisms, which may lead to abnormal excitation of central neurones [47]. The main inhibitory neurotransmitter is γ-aminobutyric acid (GABA). It has been shown that suppression of this pathway results in allodynia [48]. Within 2 weeks after a peripheral nerve injury, GABA receptor levels are reduced. Down-regulation of GABA-mediated pathways may be, in part, responsible for central sensitisation [49].

Expansion in Receptive Field Size (Recruitment)

Receptive fields of dorsal horn neurones contain subliminal areas; these represent a reservoir of activity [50]. With ongoing activation after injury there is an expansion of receptive field size leading to increased perception of pain, resulting in secondary hyperalgesia. This expansion of receptive fields does not reflect peripheral nerve or

nerve root distribution, but spinal cord architecture. It might therefore be confusing from a diagnostic point of view, as it transgresses the boundaries imposed by a hard-wired model of the CNS [51].

Immediate Early Gene Expression

Immediate changes in gene expression in dorsal horn cells occur in response to Aδ- and C-fibre stimulation. These changes persist for a variable length of time and may contribute to central neuroplasticity. Noxious stimulation mediated by Aδ- and C-fibres produces an immediate change in the expression of certain genes within the dorsal horn cells [52]. These changes are detected within minutes of stimulation and may last for months or even years. The gene c-*fos* encodes for a protein, *fos*, which forms part of a transcription factor which may control the expression of other genes which produce long-term changes in the dorsal horn. *C-fos* activation occurs as a result of increases in intracellular calcium following release of neurotransmitters like substance P and glutamate, involved in relay of nociceptive information [53]. This is followed rapidly by the appearance of *fos* protein which can be detected in laminae I, II and V of the dorsal horn. The presence of *fos* protein can be used as a marker of noxious stimulation and thus also to determine the effect of agents to reduce noxious stimulation [54].

Anatomical Re-Organisation of the Spinal Cord

Primary afferent neurones synapse in the laminae of the dorsal horn with second-order ascending neurones. Under normal conditions, Aδ- and C-fibres terminate in laminae I and II, whereas Aβ-fibres terminate in laminae III and IV. Following C-fibre injury, the large unmyelinated Aβ-fibres sprout terminals into lamina II. Aβ-fibres, which are activated by low intensity non-painful stimuli can thus stimulate the dorsal horn neurons present in lamina II, usually associated with noxious sensation [55]. This observation could explain allodynia, as Aβ-fibres form synapses with second-order neurones and their low-threshold non-noxious inputs will be signalled as nociceptive in origin. However, doubt surrounds this theory as a main mechanism of allodynia because sprouting is not fully established until 2 weeks after the injury [56]. Furthermore it has been suggested that this sprouting only occurs in a small subgroup of Aβ neurones [35].

As well as sprouting fibres into lamina II, Aβ-fibres also undergo phenotypic switching and produce the neurotransmitter substance P and calcitonin gene-related peptide [18]. These neurotransmitters are usually produced only by C-fibres, but after nerve injury their expression by C-fibres is down-regulated. Aβ-fibres begin to release these neurotransmitters at the dorsal horn following low intensity stimulation. This release of substance P can maintain the central sensitisation changes in the dorsal horn at the NMDA receptor that is usually only maintained by continued C-fibre input [56].

Contribution of Glial Cells to Pain Conditions

The last years have seen an increasing understanding of the important role that activation of glial cells and neuro-glial interactions play in the maintenance of central sensitization and thereby chronic pain conditions [57]. Microglia, astrocytes in the CNS, and also satellite glial cells in the dorsal root ganglia (DRG) and the trigeminal ganglia are involved in these processes [58]. Glial activation is primarily mediated by activation of toll-like receptor 4 (TLR4) [59]. It results in a change of glial cell morphology, increase in glial cell numbers and release of powerful pro-nociceptive mediators including ATP, cytokines and chemokines. These processes lead via neuro-glial interactions to sensitisation of CNS neurons (through activation of their cognate receptors) and thereby contribute to the phenomenon of central sensitization. As μ-opioid agonists are also glial activators, opioid-induced hyperalgesia is partially mediated through the same processes [59]; this would explain the efficacy of low-dose naltrexone in central sensitization [60]. There is now significant support for the concept that chronic pain states could be a result of a "gliopathy" [57].

21.5.2 Symptoms of Neuropathic Pain

Patients with neuropathic pain usually experience persistent and/or paroxysmal pain [61]. The pain often has an abnormal quality, for example burning, electric-shock like, shooting, lancinating or numbing. Neuropathic pain can occur in an area of neurological deficit, but might also arise from areas still innervated normally [62]. Neuropathic pain exhibits often one or more of the following characteristic features;

- *Dysaesthesia*, an unpleasant abnormal sensation, whether spontaneous or evoked.
- *Hyperalgesia*, an increased response to a painful stimulus.
- *Allodynia*, pain elicited by a normally non-noxious stimulus
- *Hyperpathia,* a painful syndrome characterised by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
- *Hypoalgesia,* diminished pain in response to a normally painful stimulus.

Clinical features of neuropathic pain are often summarised as stimulus-dependent, stimulus-independent and sympathetically-maintained pain [62].

21.5.2.1 Stimulus-Dependent Pain

Following nerve injury, increased C-fibre activity causes central sensitisation within the dorsal horn via activation of the NMDA receptor as described earlier.

Central sensitisation produces three main effects;

1. Enlargement of the sensory field of a dorsal horn neuron (secondary hyperalgesia)
2. Increase of the response to a suprathreshold stimulus (hyperalgesia)
3. Generation of a response to a subthreshold stimulus (allodynia)

These phenomena represent stimulus-dependent pain, although the relationship between stimulus and response may vary widely.

21.5.2.2 Stimulus-Independent Pain

As mentioned earlier, there are two types of sodium channels present on sensory neurons. The tetrodotoxin-resistant channels are implicated in the generation of the spontaneous pain of pathological pain states. Following injury there is reorganisation of the expression and location of the various types of sodium channel within the neuron. The tetrodotoxin-resistant channels relocate to the neuroma, where it produces areas of hyperexcitability and ectopic discharges. After nerve injury, both injured nerves and uninjured nerves close to the site of injury display spontaneous discharges. The alterations in expression of sodium channels are thought to be due to alterations in the supply of neurotrophins such as nerve growth factor and glial-derived neurotrophic factor [63].

21.5.2.3 Sympathetically Maintained Pain (SMP)

In a small but significant proportion of chronic pain sufferers, the pain has a definite sympathetic system element to it and is said to be sympathetically maintained. Following partial nerve injury in these patients, both injured and uninjured primary afferents express alpha-2 adrenoceptors on their membranes so they become sensitive to circulating catecholamines and noradrenaline release from sympathetic nerve terminals [29].

Direct coupling also occurs between the sympathetic and peripheral nervous systems with sympathetic nerves sprouting axons into the dorsal root ganglion to form baskets around the cell bodies of nociceptor neurons, where they form functional synapses. This sprouting is thought to occur under the influence of nerve growth factor. Other more central mechanisms of somatosensory-sympathetic coupling are also investigated [64].

21.6 Neuropathic Pain Syndromes

There are many causes of neuropathic pain including a number of disease states.

21.6.1 Peripheral Neuropathies

21.6.1.1 Metabolic/Endocrine

Diabetics can develop different types of neuropathies, which include polyneuropathies, autonomic neuropathy, compression neuropathy and focal neuropathies. Around 50% of diabetics have polyneuropathy and many of these present with

neuropathic pain [65]. Many diabetics, especially those with poor blood glucose control, develop a distal, symmetrical, proximally spreading and painful neuropathy [66]. Severe pain is often a feature and may be described as burning, aching or have lightning components to it. It seems that the main cause is demyelination and to a lesser extent axonal degeneration. The first stage in prevention and treatment of early neuropathies is good glycaemic control. Additionally, hyperglycaemia may have a direct effect on neuropathic pain by altering pain thresholds, tolerance and affecting opioid receptors.

Mononeuropathies, usually involve the motor supply to extraocular muscles and also nerve supply to the limbs. The third cranial nerve is most frequently affected. Pain is often a symptom. Additionally, an asymmetrical proximal, predominantly motor, neuropathy can occur, especially in older patients with poor glycaemic control [67]. Untreated hypothyroidism may result in neuropathic pain.

21.6.1.2 Toxic

Well-known neuropathies here include those caused by alcohol, chemotherapy (where the neuropathy maybe the dose limiting factor) and, more recently anti-AIDS drugs (e.g. isoniazid).

21.6.1.3 Post-infectious

The most common problem encountered is Post Herpetic Neuropathy (PHN), which increases in incidence, intensity and persistence with age [68]. The pain persists in the distribution of a peripheral nerve after herpes zoster infection (shingles). It is thought that chronic inflammatory changes result in damage to sensory nerves, resulting in deafferation of nociceptive fibres. The pain is persistent and can become intolerable with associated allodynia. Treatment is often very difficult, in particular in later stages.

21.6.1.4 Hereditary

Fabry disease, a rare lipid storage disorder, often presents with a painful neuropathy [69].

21.6.1.5 Malignant

Neuropathies can occur as a non-metastatic complication of malignant disease, usually a sensory neuropathy that can sometimes be painful. Neuropathic pain can also be caused as the result of direct tumour invasion involving nearby nerves.

21.6.1.6 Vascular

Vascular pain is a complex issue. Pain can be arterial, microvascular or venous in origin. Neuropathy can in particular follow venous insufficiency [70]. In every vascular disease, sympathetic changes may develop which contribute a neuropathic element to the ischaemic pain. The patient may develop skin hyperalgesia, dystrophic skin with a shiny appearance, muscle atrophy and vasomotor phenomena. Sympathetic blocks may be beneficial [71].

21.6.1.7 Posttraumatic

Posttraumatic neuropathies are common and can develop after any nerve injury. Even minor demyelination injuries without neurological sequelae can result in neuropathies. Examples are sciatica, neuroma or nerve entrapment after surgery or trauma, phantom limb pain, complex regional pain syndromes (CRPS) type I (without neurological deficit, previously called Reflex Sympathetic Dystrophy RSD) and Type II (with neurological deficit, previously called causalgia) and post-thoracotomy pain.

21.6.2 Central Neuropathies

Central neuropathic pain is due to a lesion or disease of the CNS [72]. These lesions may have associated symptoms that affect the patient and their pain e.g. ataxia, motor weakness and hearing/visual loss. Epilepsy and depression are also common with cerebral lesions. These aspects need to be addressed along with treatment of the pain. Central neuropathic pain is associated with spinothalamocortical dysfunction and may develop over a length of time and varies widely between individuals regardless of aetiology.

21.6.2.1 Vascular Lesions in the Brain and Spinal Cord

The aetiology here includes infarction, haemorrhage, and vascular malformation. Stroke is the most common cause of central pain due to its high incidence [73]. Around 8% of patients with acute stroke have been shown to suffer from central pain in the following 12 months.

21.6.2.2 Multiple Sclerosis

This demyelination process can result in neuropathic pain by a variety of mechanisms. Cranial nerve neuropathies, but also widespread central pain syndromes are common consequences and often difficult to treat [74].

21.6.2.3 Trauma, Tumours and Infections

Brain injury, but by far more commonly spinal cord injury, can result in a variety of central pain syndromes [75]. Syringomyelia and syringobulbia as a consequence of such injuries can cause further central pain. Tumours of the brain and spine as well as infections and abscesses can cause similar symptoms [72].

21.7 Nociplastic Pain

In 2011, the IASP changed the definition of neuropathic pain. The most relevant change was the removal of the concept of dysfunction of the nervous system from the definition [76]. This occurred in response to the increasing recognition, outlined in detail in this chapter, that most pain states change the function of the nervous system. Therefore, continued use of this definition was counterproductive, as many pain conditions fulfilled this definition, but were not the result of a lesion or disease (e.g. fibromyalgia, CRPS Type 1, nonspecific chronic back pain and many visceral and pelvic pain conditions).

This redefinition left many chronic pain conditions without an appropriate label; neurophysiologists used the term CNS dysfunctional pain states, but this is not a useful and acceptable term in clinical practice. The need for a third mechanistic descriptor besides nociceptive (inflammatory) and neuropathic pain became obvious [5]. In November 2017, the IASP decided to introduce such a third descriptor by coining the term nociplastic pain, defined as 'Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.' In parallel, the new International Classification of Diseases (ICD-11) will have chronic pain as a new entity for the first time with a subgroup labelled primary chronic pain including such nociplastic pain states [77].

21.8 Conclusion

Pain perception is a complex process. Identifying the pathophysiology of the pain presentation is important in terms of giving an explanation to the patient and the choice of management strategies.

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