PART 1 BASIC SCIENCE

OVERVIEW OF PAIN PATHWAYS 1

S.I. Jaggar

A major barrier to appropriate pain management is a general misperception that pain and nociception are interchangeable terms. This encourages the belief that every individual will experience the same sensation given the same stimulus. This is analogous to suggesting that all individuals will grow to the same height given the same nourishment – a situation that all would agree is unlikely!

Nociception is the neural mechanism by which an individual detects the presence of a potentially tissue-harming stimulus. There is no implication of (or requirement for) awareness of this stimulus.

Pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. Thus, perception of sensory events is a requirement, but actual tissue damage is not.

The nociceptive mechanism (prior to the perceptive event) consists of a multitude of events as follows:

- *Transduction*:
  This is the conversion of one form of energy to another. It occurs at a variety of stages along the nociceptive pathway from:
  – Stimulus events to chemical tissue events.
  – Chemical tissue and synaptic cleft events to electrical events in neurones.
  – Electrical events in neurones to chemical events at synapses.
- *Transmission*:
  Electrical events are transmitted along neuronal pathways, while molecules in the synaptic cleft transmit information from one cell surface to another.
- *Modulation*:
  The adjustment of events, by up- or downregulation. This can occur at all levels of the nociceptive pathway, from tissue, through primary (1°) afferent neurone and dorsal horn, to higher brain centres.

Thus, the pain pathway as described by Descartes has had to be adapted with time (see Figure 1.1).

The chapters that follow address the pathophysiological events occurring along the 'pain pathway'. It is important to recognise that all the anatomical structures and chemical compounds described are genetically coded. Therefore, to suggest that all individuals

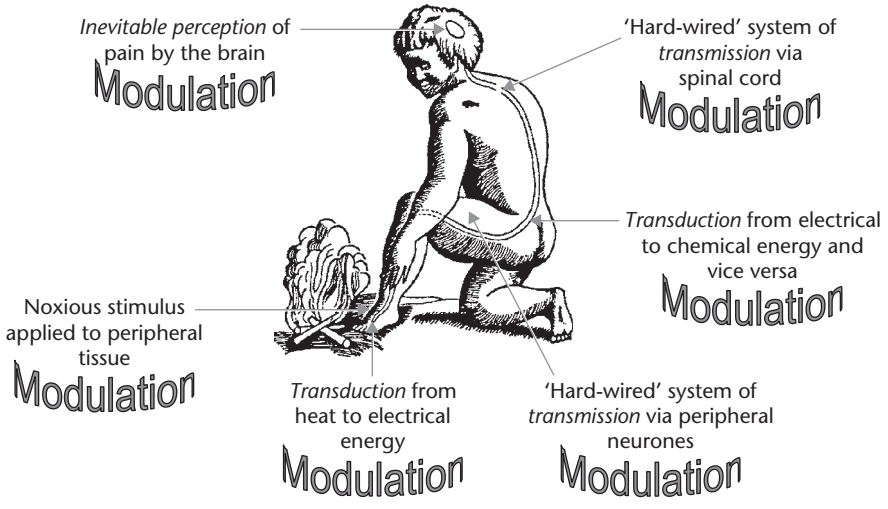

Figure 1.1 Development of the original 'hard-wired' pain pathway first described by Descartes in 1664 showing sites where modulation occurs.

will perceive pain in the same way (and if they do not they are at fault) is unsustainable.

For example, we would not suggest that eye colour is something over which people have total control – we accept that this is genetically determined. Yet, we suggest that an individual who is unfortunate enough to suffer severe pain (perhaps consequent upon the expression of particular populations of receptors responding to nociceptive chemicals) is somehow 'over-reacting' to a stimulus. Moreover, we understand that the presence of male pattern baldness requires not only the presence of a gene, but also a particular hormonal environment (high testosterone levels). Why should we be surprised, therefore, that a particular stimulus may be perceived differently in individuals with varying hormonal make-up?

This is not to suggest that all pain is entirely genetically determined, but rather it is not 'all in the mind' – a phrase often used with negative connotations in regard to pain patients. Previous experience of pain can undoubtedly alter perceptions, but this should not suggest any 'unreality'. The presence of lung cancer is frequently consequent upon prior experience – in this case, of smoking. Similarly, prior experience of pain may facilitate activity, in particular neuronal pathways, leading to a reduction in pain threshold at a later date.

A variety of tissue-damaging stimuli leads to the production of a 'chemical or inflammatory soup'. This consists of a wide variety of substances, knowledge of which is continually being expanded. Whatever the composition of this soup, pain events are generated by chemical binding with receptors on 1° afferent neurones. Such receptors consists of three major groupings: excitatory, sensitising and inhibitory. It is the balance of outcomes of these events that determines whether an action potential is generated in the neurone (Figure 1.2).

Once electrical activity is generated within the 1° afferent neurone, information is transmitted to the dorsal horn of the spinal cord. Activity is induced in the second-order neurone in a similar fashion. Quantal release of neurotransmitters from the 1° afferent neurone is dependent upon: (a) activity within the neurone, (b) external events affecting alterations in neuronal activity, for example, inhibitory and excitatory inputs upon pre-synaptic terminal. Activity in the second-order neurone is again dependent upon the balance of inputs upon it (Figure 1.3). These may arise from the 1° afferent neurone, inter-neurones or descending neurones from the brain stem and cortex.

The majority of second-order nociceptive neurones within the spinal cord cross to the contralateral side, where they synapse upon neurones in the antero-lateral aspect of the cord. Again modulation of transduction events will occur, prior to transmission in spino-thalamic pathways towards the cortical sensory centres.

While we have long considered neurological pathways to be hard wired, it is becoming increasingly clear that this is not the case. Indeed, the brain and spinal cord are able to learn and facilitate activity in commonly utilised pathways. This occurs not merely as regards useful details (e.g. how to drive a car), but also in relation to innocuous (e.g. what the blue colour looks like) and unpleasant (e.g. presence of ongoing pain in a now amputated limb) information. Thus, we should not be surprised that previous experiences can and do alter later pain perceptions. Plasticity of neuronal activity is the norm.

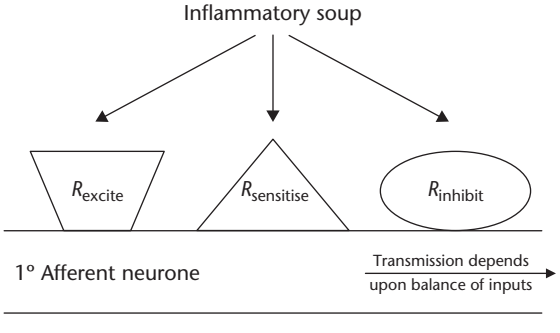

Figure 1.2 Tissue-damaging stimuli produce an 'inflammatory soup' which acts upon a variety of receptors. Onward transmission depends upon the balance of inputs affecting the 1° afferent neurone.

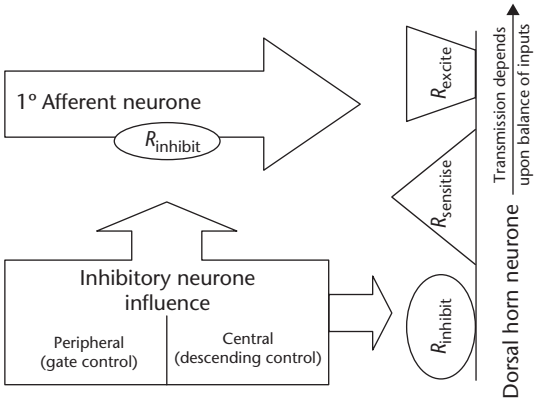

Figure 1.3 Onward transmission of information to higher centres, from the spinal cord, depends upon the balance of inputs effecting activity in the dorsal horn neurone.

The genetic basis of pain (using human and animal data to demonstrate the concepts) will be considered specifically in Chapter 4. However, when reading Chapters 2 and 3 on the peripheral and central mechanisms of pain, you should remember that the chemicals and structures described are genetically encoded, as are the receptors discussed in Chapter 8. Chapters 5–7 will deal in detail with the ways in which previous activity within the nociceptive pathways may alter current activity (and thus pain perception).

The psychological processing and consequences are central to all our human experience. Specific focus is placed on these in Chapters 13 and 47. The challenge now is to unite psychological and chemical (and thus genetic) events in an appropriate fashion when considering the problems faced by patients in pain.

PERIPHERAL MECHANISMS 2

W. Cafferty

Overview

Sensory systems are the nexus between the external world and the central nervous system (CNS). *Afferent* neurones of the somatosensory system continuously 'taste their environment' (Koltzenburg, 1999). They respond in a co-ordinated fashion, in order to instruct an integrated *efferent* response, which will retain the *homeostatic* integrity of the organism and curtail any tissue-damaging stimuli. This chapter will consider the peripheral apparatus that responds (and in some cases adapts) to a potentially injurious or noxious stimuli. Nociception forms an integral part of the somatosensory nervous system, whose main purpose can be described by *exteroceptive*, *proprioceptive* and *interoceptive functions*.

Exteroceptive functions include *mechanoreception*, *thermoception* and *nociception*. Proprioceptive functions provide information on the relative position of the body and limbs that arise from input from joints, muscles and tendons. Interoceptive information details the status and well-being of the viscera. These broad sensory modalities can be further subdivided in order to integrate more subtle stimuli (e.g. difference between flutter and vibration). In order to cope with the immense variety and magnitude of stimuli that impinge upon the CNS; sensory neurones are vastly heterogeneous and exquisitely specialized.

Heterogeneity of sensory neurones

Primary sensory neurones, whose cell bodies reside in the dorsal root ganglia (DRG), can be classified according to their cell body size, axon diameters, conduction velocity, neurochemistry, degree of myelination and ability to respond to neurotrophic factors (NTFs) (see Figure 2.1 and Table 2.1 for overview of classification). Early evidence for functional differences between populations of sensory neurones came from Erlander and Gasser who classified populations of afferents according to their conduction velocities.

Classification by size

A-fibres

A-fibres are myelinated, have large cell body diameters and can be subdivided into three further groups: Aα-, Aβ- and Aδ-fibres. Aα-fibres innervate *muscle spindles* and *Golgi tendon organs*, and determine proprioceptive function. Aβ-fibres are low-threshold, cutaneous, slowly or rapidly adapting mechanoreceptors and do not contribute to pain. Aδ-fibres are mechanical and thermal nociceptors. A-fibres generally terminate in laminae I and III–V of the dorsal horn (DH) of the spinal cord with some projection in lamina II inner (lamina IIi, see figure 2.2). They can be identified histologically by virtue of their expression of heavy neurofilament.

C-fibres

C-fibres, which constitute 65–70% of afferents entering the spinal cord, are characterized as being thinly myelinated or unmyelinated, with small diameter somata (10–25 μm), and are mainly nociceptive in function. These fibres terminate in laminae I and II, with lamina II outer (lamina IIo see figure 2.2) receiving C-fibre terminals exclusively. Afferent terminals are highly specific, both dorso-ventrally and medio-laterally. However, DH neurones can receive input from different laminae owing to their highly elaborate dendrites, spanning hundreds of microns in the dorso-ventral plane.

Neurochemical classification of sensory neurones

Sensory neurones can also be classified according to their neurochemistry, C-fibres in particular are classified as either peptidergic or non-peptidergic. Half of the c-fibre population expresses neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P (SP), somatostatin (SOM), vasoactive intestinal peptide (VIP) and galanin. The remaining unmyelinated afferents can be identified by virtue of the fact that they express cell surface glycoconjugates that bind the lectin IB4. This population also expresses the purinoceptor P_2X_3 (purine channel – responds to

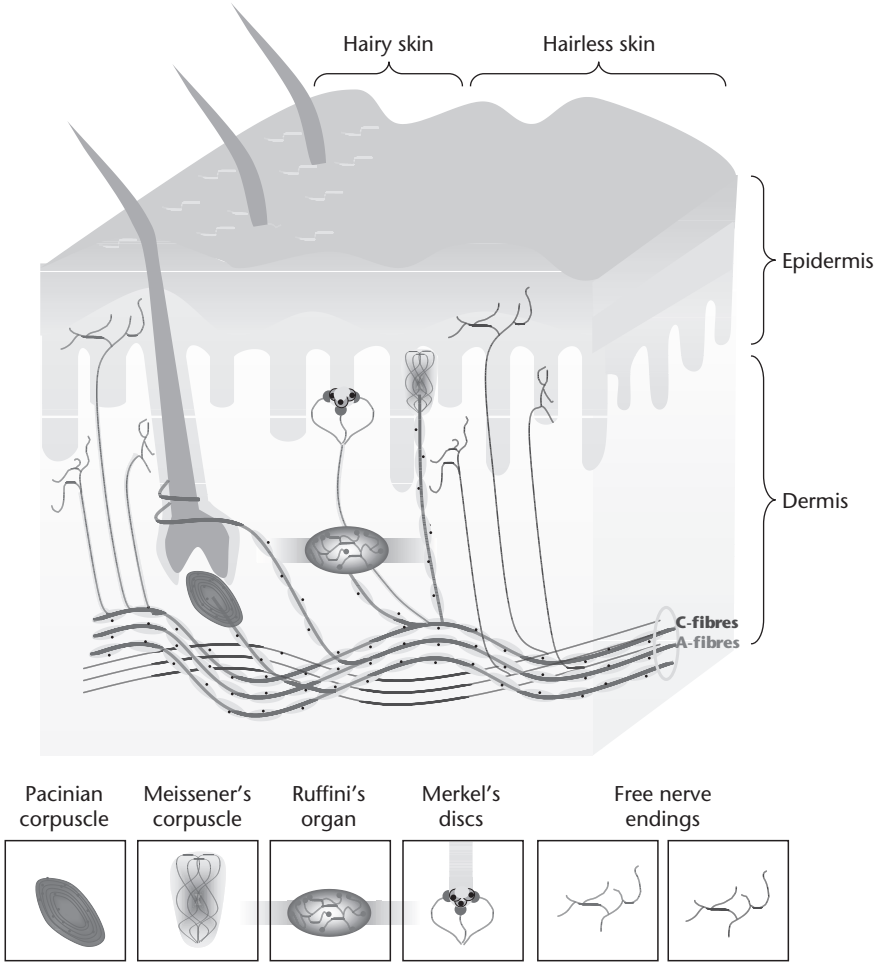

Figure 2.1 *Morphology of sensory receptors*. Receptors are found within the superficial epidermal and deeper dermal layers. Superficial receptor distribution varies between glabrous (hairless) and hairy skin. Glabrous skin presents Meissener's corpuscles, Merkel's discs and free nerve endings, while the dermal papillae of hairy skin include only Merkel's discs and free nerve endings. Subcutaneous receptors common to both glabrous and hairy skin include the Pacinian and Ruffini's corpuscles. *Meissener's corpuscles* are pressure mechanoreceptors, located on the epidermis–dermis boundary – especially on the fingertips, palm, sole of the foot and nipple. They are oval in shape and consist of many stacked, flattened Schwann cells. The nerve fibres enter the deep end of the corpuscle and are generally associated with Aβ-fibres. *Merkel's discs* are touch receptors, located in the dermis, especially of the thick skin over the palms of the hands and soles of the feet. The Merkel's discs consist of two components, the specialized Merkel's cell and a nerve ending that loses its myelination as it penetrates the epidermal basal layer. The free nerve ending forms a disc which contacts the Merkel's cell with a junction similar to a synapse. Merkel's discs are also associated with Aβ-fibres. *Pacinian corpuscles* are highly sensitive pressure receptors – approximately 2 mm × 0.5 mm located deep in the dermis, joint capsules and mesenteries. They cover nerve endings with flat fibroblast-like cells to produce sheets of 'lamellae', which contain fluid. As the Pacinian corpuscles are pressed, the fluid in the lamellae redistributes and the lamellae act as energy filters. Pacinian corpuscles are associated with Aβ nerve fibres. *Ruffini's endings* respond to tension and stretch in the skin. They are found deep in the dermis of the skin and have a thin capsule surrounding a fluid-filled cavity. This cavity contains a collagen mesh that penetrates the capsule to anchor it to the surrounding tissue. The nerve ending loses its myelination as it enters, leaving branches weaving around the collagen fibres and responding to movements of the surrounding tissue. The Ruffini's endings are associated with Aβ-fibres. *Free nerve endings* are widely distributed throughout the body, and are found as branches of unmyelinated, or lightly myelinated fibres, fasciculated beneath the epithelium. Branches of one nerve may cover a wide area and overlap the territories of others. The free nerve endings detect pain, touch, pressure and temperature, and are associated with c-fibres.

Table 2.1 Summary of receptor types

	Aβ-fibres	Aδ-fibres	C-fibres
Threshold	Low	Medium	High
Axon diameter	6–14 μm	1–6 μm	0.2–1 μm
Myelination	Yes	Thinly	No
Velocity	36–90 m/s	5–36 m/s	0.2–1 m/s
Receptor types	Mechano-receptor	Mechano/ nociceptor	Nociceptor
Receptive field	Small	Small	Large
Quality	Touch	Sharp/first pain	Dull/second pain

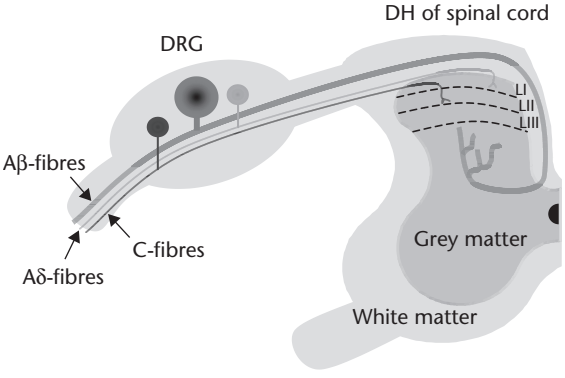

Figure 2.2 *Organization of the DH.* The central terminal projections of primary afferents are highly organized with different sub types of neurones terminating within cytoarchitectonically specific laminae. Table 2.1 above summarizes the function and properties of the three main groups. Aβ-fibres project to laminae III–IV, Aδ-fibres terminate in lamina I and c-fibres terminate in lamina in lamina II. Table 2.1 summarizes sensory neurone phenotype.

the algogen ATP) and enzyme activity of thiamine monophosphatase (TMP).

Classification by response to growth factors

Prior to propagating action potentials relating to tissue-damaging stimuli, sensory neurones have to make appropriate connections with their specific targets in the periphery, the DH of the spinal cord (Figure 2.2) and dorsal column nuclei of the brain stem. Primary sensory neurones (which are of neural crest origin) are induced shortly after the folding of the neural tube. Migration of boundary cap cells to the presumptive dorsal root entry zone (DREZ) triggers the penetration of growing sensory axons through the neuroepithelium. Large diameter axons penetrate before smaller cells.

Peripheral targets innervation depends on the availability of limited amounts of NTFs. The neurotrophic hypothesis (first proposed by Levi-Montalcini) details that survival of developing sensory neurones depends largely on factors released from their targets (Cowan, 2001). Many developing axons compete for limited quantities of targets-derived NTFs for successful development and survival. A limited number of growing fibres will receive and internalize this retrogradely supplied support. This selection process ensures appropriate targets innervation and the elimination of inaccurate projections. Thus, it is accepted that cell death is normal in the process of the development of the nervous system.

Sub-populations of sensory neurones have exquisite sensitivity to trophic factors, owing to a differential expression of high-affinity NTF receptors. The small diameter peptidergic c-fibre population expresses the high-affinity nerve growth factor (NGF) receptor tyrosine kinase A (TrkA). The non-peptidergic fibres express receptor components for another family of NTFs, namely the glial cell line-derived NTF (GDNF) receptor GFRα1–4 and their cognate signalling kinase domain c-ret. The large diameter A-fibres express the high-affinity receptor for neurotrophin-3 (NT3), TrkC. Sensory neurones retain their ability to respond to NTFs during adulthood, where they mediate:

- Homoeostatic functions under physiological conditions.
- Sensitization after injury or inflammation (see Chapter 6).

Properties of peripheral receptors

Mechanoreceptors

Mechanoreceptors, which respond to tactile non-painful stimuli, can be assessed psychophysically by the ability of a human subject to discriminate whether application of a two blunt-point stimuli is perceived as one or two points (by varying the distance between the points). These receptors are divided into two functional groups (rapidly or slowly adapting) depending on their response during stimuli. Rapidly adapting mechanoreceptors respond at the onset and offset of the stimuli, while slowly adapting mechanoreceptors respond throughout the stimuli duration. Mechanoreceptors (see Figure 2.1) can be divided into those expressed in:

- Hairy skin (hair follicle receptors):
  - Low threshold, rapidly adapting.
  - Three major subtypes: ‘down’, ‘guard’, tylotrich’.

- Glabrous (hairless) skin:
  - Small receptive fields.
  - Two major subtypes: 'Meissener's capsule' (rapidly adapting) and 'Merkel's disc' (slowly adapting).

Proprioception (limb position sense), which refers to the position and movement of the limbs (kinesthesia), is determined by mechanoreceptors located in skin, joint capsules and muscle spindles. The CNS integrates information received from these receptors, while keeping track of previous motor responses that initiated limb movement – a process known as *efferent copy* or *corollary discharge* (reviewed by Matthews, 1982).

Cutaneous nociceptors

Cutaneous receptors that respond to relatively high magnitude or potentially tissue-damaging stimuli are termed *nociceptors*. They can respond to all forms of energy that pose a risk to the organism (e.g. heat, cold, chemical and mechanical stimuli). Unlike other somatosensory receptors, nociceptors are free nerve endings and are, therefore, unprotected from chemicals secreted into, or applied onto, the skin. The evolutionary strategy employed to cope with such a complex barrage of inputs has determined that some nociceptors are dedicated to respond to one stimuli (i.e. thermoception or mechanoception) and others to a range of stimuli modalities (hence termed polymodal). Further complexity lies in the observation that excitation of nociceptors does not always result in the sensation of pain – having an affective component which can alter depending on mood.

A number of different techniques have been employed in order to study the properties of nociceptors. The most convincing are microneurographical recordings of receptive fields of single afferent fibres in conscious human subjects, allowing correlation of afferent discharge and perception of pain (Wall and McMahon, 1985). Early studies used only mechanical and thermal stimuli to probe the properties of nociceptors, hence the common nomenclature of CMH and AMH for C- and A-fibre mechano-heat-sensitive nociceptors. This is a perilous differentiation, as more recent evidence suggests that most nociceptors responding to heat and mechanical stimuli will also respond to chemical stimuli.

C-fibre mechano-heat-sensitive nociceptors

These fibres are considered polymodal, as they respond to mechanical, heat, cold and chemical stimuli. Their monotonic increase in activity evokes a burning pain sensation at the thermal threshold in humans (41–49°C). CMH responses are affected by stimuli history and are subject to fatigue and sensitization modulation (see later and chapter 5 on hyperalgesia).

A-fibre mechano-heat-sensitive nociceptors

Activation of these receptors is interpreted as sharp, prickling or aching pain. Owing to their relatively rapid conduction velocities (5–36 m/s), they are responsible for *first pain*. Two subclasses of AMHs exist: types I and II.

- Type I fibres respond to high magnitude heat, mechanical and chemical stimuli and are termed polymodal AMHs. They are found in both hairy and glabrous skin.
- Type II nociceptors are found exclusively in hairy skin. They are mechanically insensitive and respond to thermal stimulation in much the same way as CMHs (early peak and slowly adapting response) and are ideally suited to signal the first pain response.

Deep tissue nociceptors

Our vast understanding of cutaneous nociceptors has lead to increased interest in understanding the complex activity of nociceptors in deep tissues. Activity of nociceptors not only depends on the origin and nature of the stimuli, but also in what tissue the receptor is located. Knowledge of how activity from nociceptors causes pain arising from deep tissues, such as muscle, joints, bone and viscera remains incomplete. Unlike cutaneous pain, deep pain is diffuse and difficult to localize, with no discernable fast (first pain) and slow (second pain) components. In many cases deep tissue pain is associated with autonomic reflexes (e.g. sweating, hypertension and tachypnoea). Nociceptors in joint capsules lack myelin sheaths. They are a mixed group of fibres, some of which have a low threshold and are excited by innocuous stimuli, while others have a high threshold and are activated by noxious pressure exceeding the normal articular range. Units that do not respond to mechanical stimuli have been termed *silent nociceptors*.

Silent nociceptors are also present within the viscera. Silent visceral afferents fail to respond to innocuous or noxious stimuli, but become responsive under inflammatory conditions. Visceral afferents are mostly polymodal C- and Aδ-fibres. In contrast to the joint, these afferent fibres have no terminal morphological specializations and are consequently sensitized to chemical mediators of inflammation and injury.

Peripheral mechanisms of injury-induced or inflammatory pain

Nociceptor activation is dynamically modulated by the magnitude of stimuli. Therefore, it is not surprising that supra-threshold or tissue-damaging stimuli alter subsequent nociceptor responses. Overt tissue damage, or inflammation, causes the sensation of pain. The most common symptom of on-going or chronic pain states is tenderness of the affected area. This tenderness, or lowered threshold for stimulation-induced pain is termed *hyperalgesia*. Hyperalgesia associated with somatic or visceral tissue injury can be assessed experimentally by observing how the response characteristics of a given fibre alter after a manipulation causing hyperalgesia. Hyperalgesia, or lowered-threshold to thermal and mechanical stimuli, occurs at the site of trauma (*primary hyperalgesia*). Uninjured tissue around this area also becomes sensitized, but to mechanical stimuli only (secondary hyperalgesia or allodynia). Divergent mechanisms mediate these phenomena. Simple cutaneous assessments have revealed the location of the neural mechanism that mediates both primary and secondary hyperalgesia. The experimental protocol is demonstrated in Figure 2.3. These experiments have illustrated that primary hyperalgesia has a major peripheral component, while the mechanism that mediates secondary hyperalgesia resides within the CNS (see Chapter 5).

Peripheral *sensitization* mediates primary hyperalgesia to thermal stimuli. Campbell and Meyer illustrated that CMHs become sensitized to burn injuries in hairy skin, but fail to do so in glabrous skin, where AMHs become sensitized for heat hyperalgesia. However, primary hyperalgesia to mechanical stimuli does not result from sensitization of either CMHs or AMHs – thresholds to mechanical stimuli (using graded von Frey filaments) being unchanged by heat or mechanical injury. Mechanical primary hyperalgesia arises as a result of receptive field expansion. Both CMHs and AMHs modestly sprout into adjacent receptive fields resulting in a greater number of afferent units being activated after mechanical stimuli (with spatial summation causing increased pain).

Sensitization of nociceptors: inflammation

Tissue injury results in complex sequelae procured in part by the recruitment of inflammatory mediators. The inflammatory reaction rapidly proceeds in order to remove and repair damaged tissue after injury. Pain develops in order to protect the organism from further damage. The affected area typically becomes:

- Red (*rubor*).
- Hot (*calor*): as a result of increased blood flow.

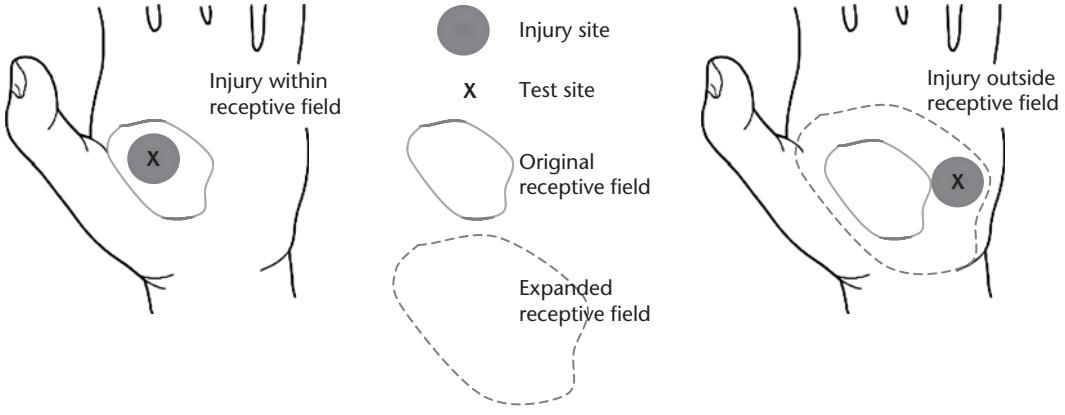

Figure 2.3 *Sensitization: primary hyperalgesia.* Hyperalgesia is defined as a leftward shift in the stimulus response function that relates magnitude of pain to stimulus intensity. This is illustrated in humans who report a lower pain threshold following burn injury. The experimental protocol commonly engaged to identify the mechanism of primary and secondary hyperalgesia is illustrated above. Firstly the response characteristics of a single fibre are established (usually response to mechanical stimulation to allow for mapping of the receptive field), subsequently the skin undergoes a manipulation (injury) that causes hyperalgesia; the test site is then re-assessed for alterations in response characteristics. Sensitization at the site of injury (i.e. of damaged tissue) is termed primary hyperalgesia, whereas sensitization outside the injury site is termed secondary hyperalgesia. If the above protocols are engaged (i.e. both test site and injury site coincide) then nociceptors are observed to have an increased response to the test stimulus, therefore primary hyperalgesia must have a significant peripheral component. However if the test stimulus and injury site do not coincide, then nociceptors fail to become sensitized; therefore the mechanism for secondary hyperalgesia must reside in the CNS.

- Swollen (*tumor*): due to vascular permeability.
- Functionally compromised (*function lasea*).
- Painful (*dolor*): as a result of activation and sensitization of primary afferent nerve fibres.

Sensitization occurs due to the release of chemical inflammatory mediators from damaged cells. A number of mediators directly activate nociceptors, while non-nociceptive afferents remain unaffected. Others act on local microvasculature causing the release of further chemical mediators from mast cells and basophils, which then attract additional leucocytes to the site of inflammation. Each of these mediators will be considered individually.

Chemical sensitivity of nociceptors

The action of injury-induced or inflammatory chemical mediators is attributed to the presence of their cognate receptors on primary afferent terminals. Figure 2.4 illustrates the location of these receptors and the possible origin of their respective ligands.

Factors that mediate the sensitivity of nociceptors, while predominantly originating from non-neuronal-damaged cells, can also emanate from the afferent terminal itself. This phenomenon is termed an *efferent nociceptor function* or *neurogenic inflammation* (for review see Black, 2002). Neurogenic inflammation is typified by two cutaneous reflexes:

- Vasodilatation (observed as a penumbral flare at the injury site).
- Plasma extravasation (observed as a wheal around the injury site).

Both of these processes are mediated by the release of neuropeptides (e.g. SP and CGRP) from primary afferent terminals (review see Richardson and Vasko, 2002).

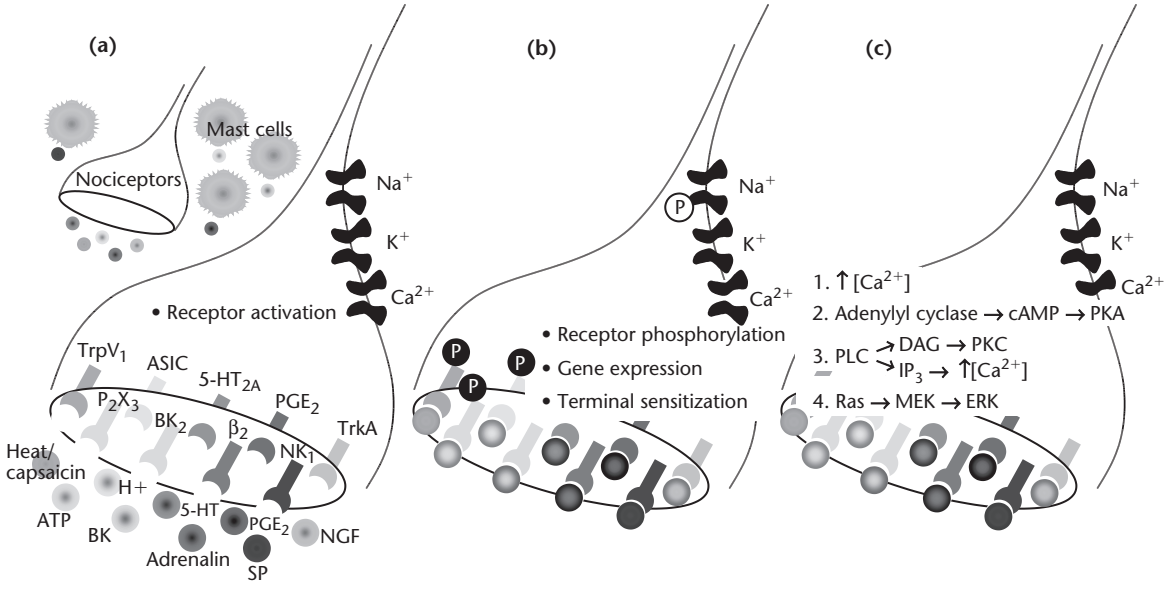

Figure 2.4 *Summary of nociceptor activation and sensitization.* Tissue damage or inflammatory insults intensify our pain experience by increasing the sensitivity of nociceptors to both thermal and mechanical stimuli. This figure summaries the mechanisms whereby the peripheral apparatus of the nociceptive pathway (the primary afferent), exacerbates this sensation. (a) Chemical mediators including ATP, BK, 5-HT, epinephrine, PGE_2, NGF and SP are released from axon terminals, damaged skin, inflammatory cells and the microvasculature surrounding the injury site. The injury site is typically very acidic owing to the increased concentration of protons in the immediate area. (b) Each of these chemical mediators bind to their high-affinity cognate receptor, present on nociceptive afferent terminals. The nociceptor-specific receptor for the irritant capsaicin, TRPV1 is also present on terminals and transduces noxious thermal stimuli. Receptor activation results in terminal sensitization or plasticity, either immediately via a post-translational mechanism (e.g. receptor phosphorylation TRPV1, P_2X_3 or ion channel phosphorylation PGE_2 or BK-mediated Na^+ phosphorylation) or over a prolonged time course which requires gene expression (NGF). (c) The pathways activated by these ligands include elevating intracellular $[Ca^{2+}]$ ([1] ASIC, P_2X_3, TRPV1), activating G-protein-coupled receptors ([2 and 3] PGE_2, BK, β_2) and subsequently elevating cAMP then PKA or elevating intracellular Ca^{2+} via PLC or the Ras-MEK–ERK/MAP-kinase pathway ([4] NGF). These pathways converge to alter the excitability of the nociceptor, ultimately lowering its threshold for activation and resulting in an increased pain sensation.