

# Diagnosis and Management in Patients with Chronic Pelvic Pain Syndrome



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By

Jörgen Quaghebeur  
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## SUMMARY

Chronic pelvic pain (CPP) involves a list of deviations with persistent pain in the pelvic area as the main factor. Multiple pain syndromes exist and after assessment, often the reason for the chronic symptoms remains unclear.

The exclusion of curable pathology that causes pain is of the highest importance. When no reasons for the pain are found, or when the pain cannot be cured, symptomatic treatment will be necessary.

The most successful treatment is a multidisciplinary approach. Doctors, nurses, physical therapists, osteopaths, psychologists and other disciplines can be of help.

The chronic pain has an essential impact on the quality of life, and substantial negative consequences on the psychologic and emotional state of these patients. The success of the treatment is not easy to predict. Usually, it will be long term.

After a general discussion, the pain-related abnormalities in most parts of the small pelvis are described, and specific treatments discussed separately. Ample attention is given to the psychologic approach.



# CHAPTER 1

## INTRODUCTION

Chronic pelvic pain (CPP) is a challenging health problem. In the small pelvis and the perineal area multiple tissues, structures and organs can all play a causal role, influence each other and together determine the clinical picture of what often becomes a long-lasting pain syndrome.

The chronic aspect of the pain needs a different approach to that in acute pain.

This book aims at being a practical guide for everybody involved in CPP: health care providers and patients.

Right from the beginning, it must be clear that, partly due to late diagnosis, a person suffering from CPP passes through a very negative experience with important corporal, psycho-emotional and social impacts.

When providing therapeutic help, a therapist must realise that knowledge is essential, and a lot of patience and empathy mandatory. There is little hope for quick success, and the result remains unclear. While it is not realistic to promise a complete cure, the patient can be told that pain can be made less, and the quality of life improved. It is best to start treatment on this basis.

The authors

## CHAPTER 2

### GENERAL CONSIDERATIONS

#### 2.1 Sensation and pain

##### 2.1.1 Sensation

The bodily sensation is a perception of stimuli running to the brain through activated nervous pathways. Everywhere in the human body, receptors are present that can detect changes and send information upwards for further processing and eventually start a reaction. We can feel our heartbeats, movement of the bowel or desire to void. Sensory receptors are present in all structures and tissues. Different receptor types exist, and they all have their specific function. Some detect normal activities and status of the body; others inform about threat and harm. From their detection area, sensory signals are sent to the spinal cord, and further to the midbrain and sensory cortex. This transport is by electric action potentials and chemical processes with the release of mediators that can inhibit or excite other nerve fibres.

The sensory pathway fibres consist of first-order neurons from the stimulus site to the spinal cord, second-order neurons from the spinal cord/brainstem to the thalamus, and third-order neurons from the thalamus to the sensory cortex of the brain (Figures 2.1, 2.2).

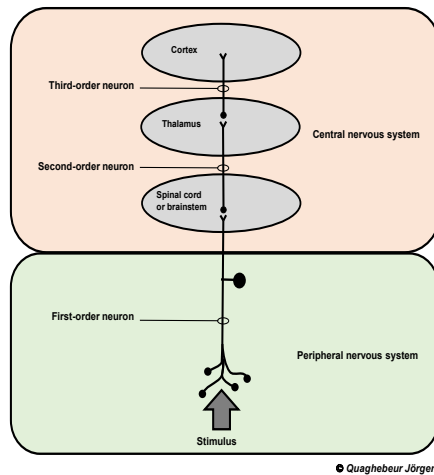
The thousands of signals originated in the entire body are continuously determined, evaluated, interpreted, sent further for central actions or are inhibited. During their progress in the afferent direction, they can provoke reactions that are related to the initial stimulus, even before something gains our attention. The withdrawal reflex touching a heated object can be an example.

Fortunately, most of the sensory information does not reach consciousness. Only a minor fraction does, and guides many of our daily life functions.

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Transmission of sensory information

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**Figure 2.1: The transmission of stimulus information through different order neurons to the brain**

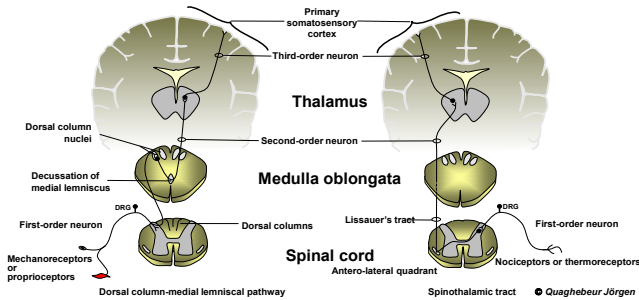
### 2.1.2 Sensation of the pelvic organs

Just like the rest of the human body, organs have receptors and nerve pathways. They receive stimuli (e.g. filling, contraction, injury) that, when sent to the central nervous system (CNS), can provoke viscerosensory and visceromotor reactions. Some receptors send information about the chemical composition of tissues. For the organs in the small pelvis (e.g. urinary bladder, distal gut, gender organs) sensation is needed to permit some conscious regulation of autonomically innervated structures. The afferent information from organs is also a continuous process but happens mostly unconsciously. When certain thresholds are reached, the specific sensation will appear and help to start processes such as micturition or defecation.

---

## Sensory pathways

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DRG: dorsal root ganglion

---

**Figure 2.2: Pathways transmitting sensory information**

## 2.2 Pain

### 2.1.1 Definition

Pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (Merskey and Bogduk 1994b). Pain can also be described as: “... whatever the experiencing person says it is, existing whenever the experiencing person says it does” (McCaffery and Beebe 1989). Recently, another description of pain has been proposed that is compatible with the International Association for the Study of Pain (IASP) definition: “Pain is a mutually recognisable somatic experience that reflects a person’s apprehension of threat to their bodily or existential integrity” (Cohen et al. 2018). The subjective description of pain by an individual becomes adapted for clinical evaluation by others (Cohen et al. 2018). There has been quite some debate about this definition, and the reader should look at the IASP ICD-11 publications (Treede 2018; Aziz et al. 2019; Nicholas et al. 2019).

It is essential to realise that pain is a complex experience that integrates affective, cognitive and behavioural factors with extensive neurobiology (Li



and Moore 1998; Clark and Cox 2002; Murinson et al. 2011; Bushnell et al. 2013). Figure 2.3 shows the definition of acute and chronic pain.

---

### Definition of pain

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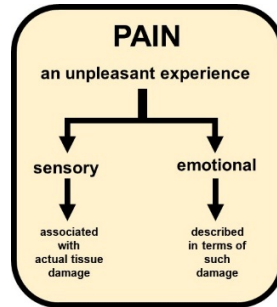
#### Why not merely “pelvic pain”?

##### - ACUTE pelvic pain

Symptoms of underlying tissue injury and disease

##### - CHRONIC pelvic pain

Becomes the disease, in its own right, with generalised symptoms




---

***“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” \****

\* IASP

---

**Figure 2.3: Definition of pain**

### 2.2.2 Acute pain

Acute pain arises suddenly, and mostly a reason for the pain can be easily found (e.g. injury, contusion, inflammation). The awareness and the degree of pain experience depend on multiple factors. Acute pain disappears or diminishes when sharp aggression stops, and healing occurs.

### 2.2.3 Chronic pain

Pain is chronic when it persists for an average period longer than six months. In non-malignant pain, three months is the difference between acute and chronic pain (Merskey and Bogduk 1994a). Chronic pain is not merely sustained acute pain, but the result of the modulation of structural and functional factors involved in perception and behavioural processing. Plasticity arises because of structural remodelling and reorganisation of synapses, cells and circuits. This process evolves from the peripheral to

central to cerebral level if the pain continues to be felt (Kuner and Flor 2017).

Chronic pain involves complex neural networks that include sensory, emotional, cognitive and interoceptive processing (Craig 2006; Simons et al. 2014) and if the suffering continues for some time, the pain will not always stop if the cause of pain disappears (Meyer et al. 2006). The chronic aspect of the pain results in an altered psychological status, and the psychological impact on the pain perception should not be underestimated (Navratilova et al. 2016).

A cross-sensitisation can occur due to a common innervation of different organs, and cutaneous and musculoskeletal relations. Chronic pain is typically variable in intensity, exhausting, poorly localised and causes a decreased level of health-related quality of life. These influencing factors – nerve plasticity, sensitisation – have to be taken into account when dealing with CPP (Craig 2006).

Pain is a sensation that comes from “inside the body”. Everywhere in the body detectors exist to evaluate and notice damage (e.g. nociceptive receptors). The first step starts at free nerve endings which are stimulated by tissue damage, compression and inflammatory products, e.g. prostaglandins. The pelvic pain peripheral nerves run upwards in the dorsal horn and spinothalamic tract in the spinal cord, where they synapse and attain higher centres. Substance P is released at the level of the synapse, which activates the next neuron.

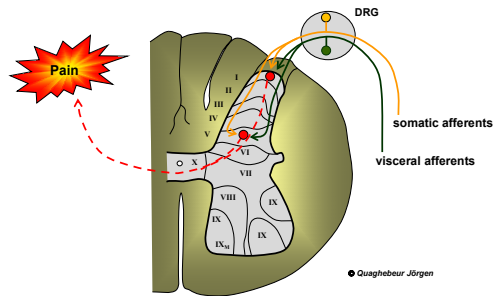
This information is transmitted via different types of nerve fibres. Impulses can reach the thalamus and sensory cortex via myelinated A $\beta$  (pressure, touch, proprioception, nociception), A $\delta$  and C-fibres. A $\delta$  fibres have a myelin sheath, transport quickly and give acute, sharp and localised pain. In the case of stimulation of different nerve types simultaneously, this sensation comes first. C-fibres are thin, do not possess a myelin sheath, transport the stimuli slowly and provoke a dull, diffuse, burning pain. These fibres connect with the reticular formation, the hypothalamus and the limbic system. C-fibre pain occurs in a second phase, remains for a more extended period and is unpleasant and exhausting. When reaching the sensory cortex, the pain impulses are felt; the passage through the central brain adds emotion to the perception. With time, the pain sensation disappears spontaneously because of the endogenous opiates that are produced in the periaqueductal grey and reticular formation in the brainstem, which inhibit the impulse transmission (Fields et al. 2006). Both musculoskeletal and visceral sensors run to the dorsal horn, resulting in a viscerosomatic convergence via circuits that connect different parts in the zones of Rexed. Figure 2.4 shows the viscerosomatic convergence of primary afferent fibres

on laminae I and V neurons of the dorsal horn. The dorsal horn is a processing station, with complex connections where modulation of the nociceptive input occurs (Terman and Bonica 2001; Todd and Koerber 2006). Pain runs through the lateral spinothalamic tract.

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### Viscerosomatic convergence of primary afferent fibres in the dorsal horn

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**Figure 2.4: Viscerosomatic convergence of primary afferent fibres in the dorsal horn**

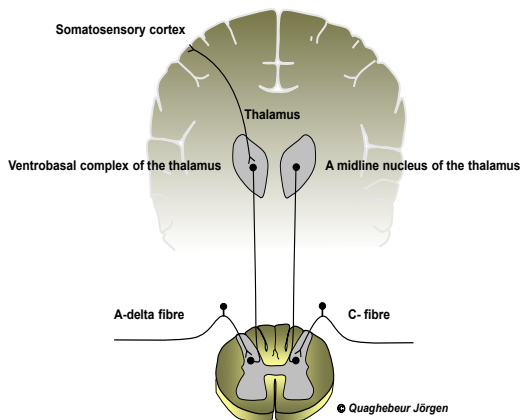
The difference must be made between pain caused by direct stimulation of the receptors (e.g. crushing or inflammation of tissue) and neuropathic pain that is caused by an injury of the peripheral nerves or CNS. Quite often, these occur together. When a bladder tumour grows into the bladder wall, or when the bladder wall is directly injured or suffering from very aggressive inflammation/infection, the bladder pain is the result of both the degradation of the bladder tissue with the free pain nerve endings and the direct penetration, compression and damage of the nerves in the bladder wall.

Different coding systems determine the central interpretation of pain stimuli. One coding results from the type of receptor. If no specific receptors exist the stimulus is coded, followed by interpretation of the signals in the brain. There is also coding for stimulus intensity (quantity of provoked action potentials) and for the area where the stimulation occurs. Figure 2.5 shows the afferent pathways that conduct stimuli via A $\delta$  and C-fibres.

---

Afferent nerve fibres

---



**Figure 2.5: Overview of stimuli transport of A-delta and C-fibres**

The sensory information from the pelvic area is strongly influenced by the complex local anatomy, the joint innervation of different organs and the crosstalk between these structures. It means that the clinical approach in cases of chronic pelvic pain is never easy.

The sensitisation processes can also induce an increase in the perception of normal stimuli so they are felt like pain (allodynia). In contrast, painful stimuli can provoke much more severe pain than expected (hyperalgesia). Table 2.1 summarises the role of different nerve fibres in pain stimuli transport.

**Table 2.1: Types of sensation transported through different nerve fibres of the pelvic region**

---

Sensory nerve fibre types			
	Mechanoreceptors	Thermic receptors	Nociceptors
<b>A<math>\beta</math> fibres</b>	+		+
<b>A<math>\delta</math> fibres</b>	+	+	+
<b>C-fibres</b>	+	+	+

---

Fibre type, the location of the receptors, the function of the receptors and inflammatory mediators all influence pain mechanisms and bladder

dysfunction. The fibre types in the lower urinary system, their location in the bladder wall, the normal function and the effect of inflammatory mediators are summarised in Table 2.2.

**Table 2.2: Fibre types in the lower urinary system, location, normal function and effect of inflammatory mediators**

Fibre type	Location	Normal function	Effects of inflammatory mediators
A-delta (finely myelinated)	Muscle	Respond to muscle wall tension	Increased discharge during distension and lowered thresholds
C-fibre (unmyelinated)	Epithelium	Respond to stretch of the epithelium (bladder volume sensors)	Increased discharge during distension and lowered pressure threshold
C-fibre (unmyelinated)	Epithelium	Insensitive to normal distension (“silent afferents”)	Afferents become mechanosensitive thereby unmasking a new afferent pathway during inflammation
C-fibre (unmyelinated)	? Epithelium ? Muscle ? Serosa	Sensitive to overdistension (nociceptors)	? Sensitive to some irritants
C-fibre (unmyelinated)	? Epithelium ? Muscle	Respond to cold stimulation, insensitive to normal bladder distension (“cold receptors”)	

Modified from Morrison (1987): Morrison JFB. Sensation arising from the lower urinary tract. In: *The physiology of the lower urinary tract* (Torrens M, Morrison JFB, eds) London Springer 1987: pp 89-131 (Morrison 1987).

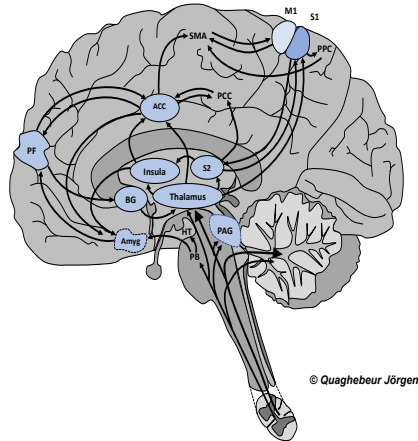
?: supposed but uncertain – further research is needed.

Figure 2.6 and Table 2.3 show the different regions of the brain involved in pain perception.

---

### Neuroanatomy of brain areas involved in pain perception

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HT, hypothalamus; Amyg, amygdala; PAG, periaqueductal grey; PF, prefrontal cortex; BG, basal ganglia; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; PPC, posterior parietal cortex; M, motor; S, sensory; SMA, supplementary motor area; PB, pineal body.

---

Adapted from: Price DD. 2000. Psychological and neural mechanisms of the affective dimension of pain. *Science*. 288(5472): 1769-72 and Apkarian AV et al. 2005. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*. 9(4): 463-84.

---

### Figure 2.6: Neuroanatomy of brain areas involved in pain perception

Multiple areas in the brain are involved in the functioning of the bladder, pelvic floor and pain mechanisms. These areas all have specific properties and are interconnected. They are related to different functional aspects (e.g. location of pain, awareness, emotional components, determination between safety and threat, stress), of the brain in relation to bladder physiology and pain.

**Table 2.3: Brain regions involved in pain perception**

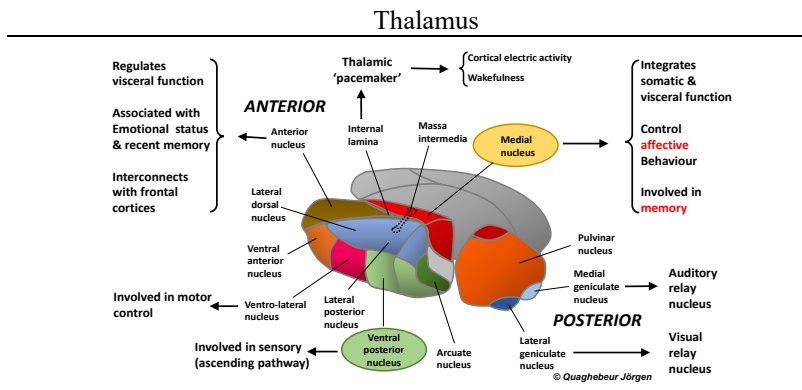
Brain regions involved in pain perception
Limbic Paralimbic Anterior cingulate cortex Insular cortex Prefrontal cortex Primary and somatosensory cortices

Table 2.4 summarises the different aspects of pain perception related to brain functioning.

**Table 2.4: Central handling of pain**

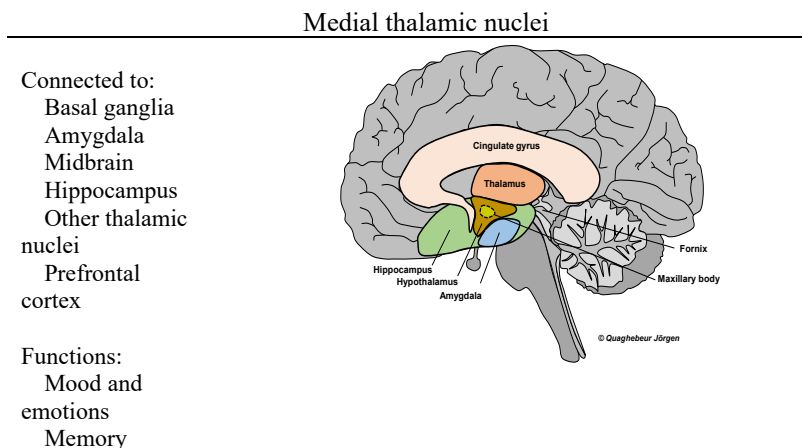
Central handling of pain
Distinguishing location and quality of the pain: Topographic organisation in the somatosensory cortex for nociceptive potentials Visceral versus cutaneous pain: activation parts network Side of the body: somatosensory cortex Attentional and emotional: anterior cingulate cortex

The thalamus has a central role in pain interpretation, and its connection to cortical and limbic structures is essential for pain perception. Figure 2.7 shows the nervous connections of the thalamus.



**Figure 2.7: The thalamus and its nervous connections**

The medial thalamic nuclei link with different areas in the brain, explaining the relation between pain, functioning of the bladder and emotional aspects. Figure 2.8 shows the medial thalamic nuclei.



**Figure 2.8: Structures of the midbrain**



### 2.2.4 The effects of a lesion

At the level of the tissue lesion pain modulators are released such as potassium, serotonin, bradykinin, prostaglandins and substance P. As a result, dilatation of the peripheral blood vessels occurs. In the mast cells, histamine is released which increases the vasodilatation and excites the nerve ending (McMahon et al. 2006; Woolf and Salter 2006). (Figure 2.9)

#### Effects of injury

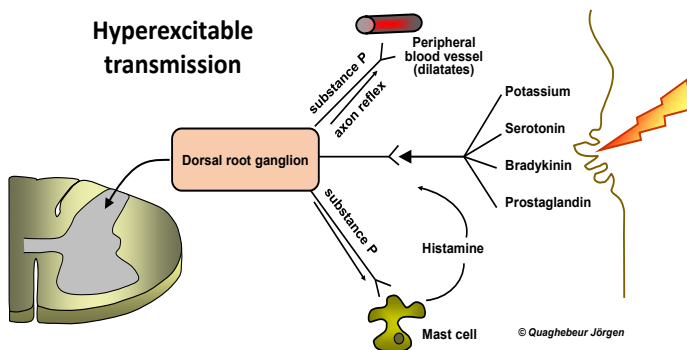


Figure 2.9: Effects of a lesion

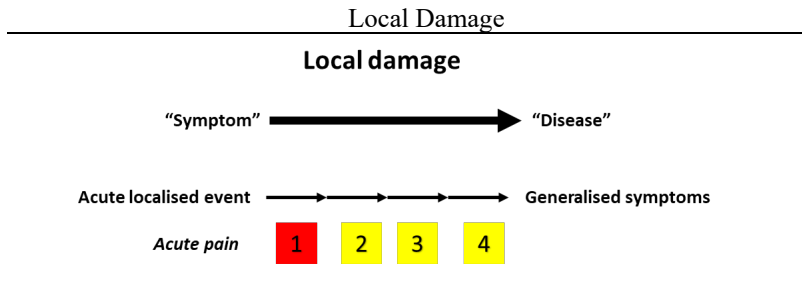
### 2.2.5 The process of sensitisation

#### 2.2.5.1 Step 1: peripheral stimulation

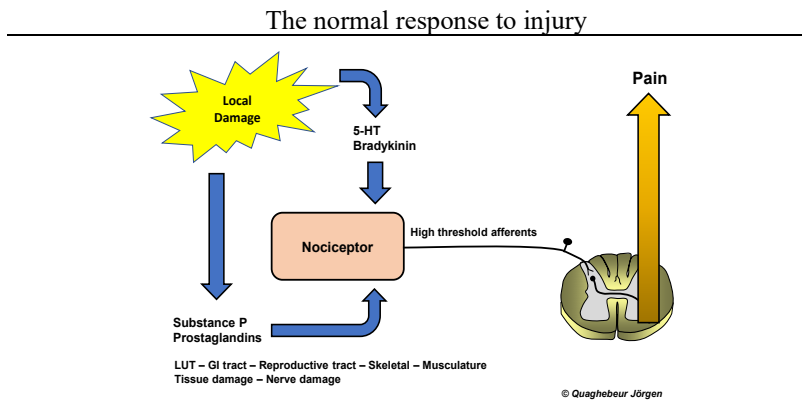
Permanent pain stimulation can sensitise the nervous system, and thereby disturb the normal pain response. Prolonged stimulation of the nociceptors (LTP) causes further release of more pain modulators, and the CNS is sensitised (McMahon et al. 2006). In the case of neurogenic inflammation, the uninjured nerve fibres are activated as well, and the sodium channels stimulated. Also, necrosis of neurons excites the nervous system with loss of the central inhibition as a result.

Peripheral sensitisation of the A $\delta$  and C-fibres can maintain chronic pain. Experimental inflammation of hollow organs demonstrated sensitisation reactions of the mechanosensitive visceral afferents and also activation of the “silent” afferents. Sensitisation is often accompanied by a

decreased sensory threshold and/or increased spontaneous activity (Gebhart 2000). Figures 2.10 and 2.11 show the processes during evolution after a local injury or inflammation.



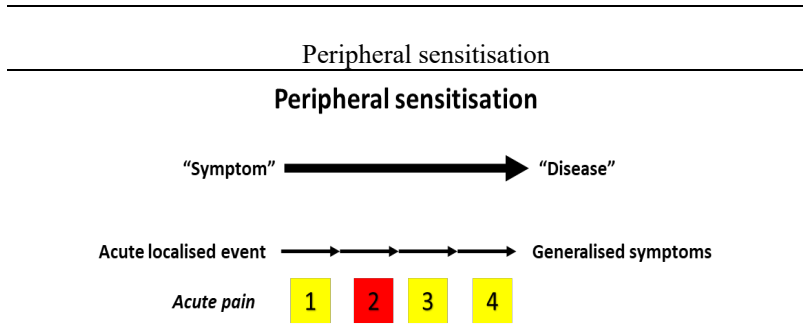
**Figure 2.10: Step 1, local damage**



**Figure 2.11: Pain-causing mechanism when there is local damage**

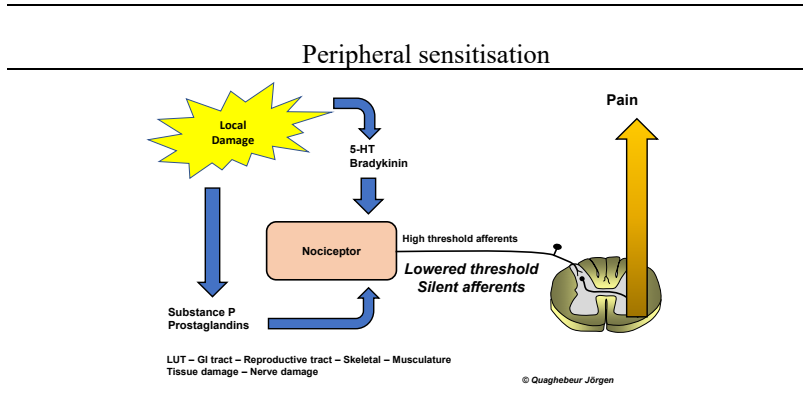
### 2.2.5.2 Step 2: peripheral sensitisation

Figures 2.12 and 2.13 show the installation of peripheral sensitisation following prolonged pain and inflammation.



**Figure 2.12: Step 2 peripheral sensitisation**

Figure 2.13 shows that continuous pain will lower the pain thresholds and activate the silent afferents or wide range dynamic neurons installing central sensitisation.



**Figure 2.13: Peripheral sensitisation mechanisms in chronic pain**

As a result of tissue injury substance P and prostaglandins are released, triggering the release of chemicals and installing an inflammatory reaction that disturbs the transmission of pain signals to the brain. Chronic pain and stimulation of inflammatory pain mediators are mainly carried by thin unmyelinated nociceptors (C-fibres) that synapse with neurons in the dorsal horn of the spinal cord (Brookoff 2000, 2006).

### **2.2.5.2.1 Activation of NMDA receptors**

Glutamate is the primary neurotransmitter in nociceptors synapsing with the dorsal horn of the spinal cord and activates the NMDA (N-methyl-D-aspartate) receptors, but can also bind with other receptors. Activation of NMDA receptors in the long term will cause wind-up. As a result of this, spinal neurons carrying pain will be activated with less peripheral stimulation. Less glutamate is necessary to transmit nociceptive stimulation, and more antinociceptive input is needed to inhibit the pain. Endorphins and other naturally occurring pain relievers will be insufficient and lose their effectiveness. Continued activation of NMDA receptors and plasticity will also install new nerve fibre endings and connections (sprouting), emphasising pain sensation. Plasticity, neural remodelling and new fibre connections may activate the reticular centre accenting the emotional component of pain (Brookoff 2000, 2006).

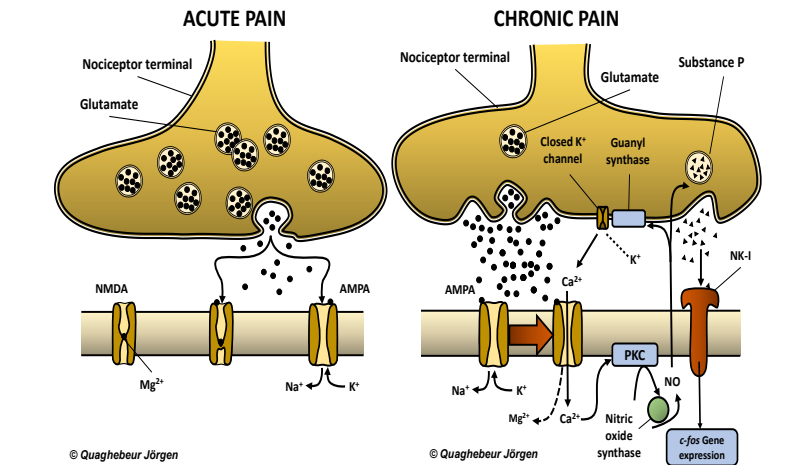
### **2.2.5.2.2 Activation of AMPA receptors**

The AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic-acid) receptors are mainly involved in the sensation of acute pain and are always activated on afferent nerve endings. The NMDA receptors only become functional as a result of persistent or excessive release of glutamate. As a result of continued activation of AMPA receptors, magnesium ions that generally regulate the transmembrane sodium and calcium channels of the NMDA receptor complex become disturbed as well. Changes in the neuronal membrane receptors initiate the central hypersensitisation and are the primary reason for the transition from acute to chronic pain (Brookoff 2000, 2006).

### **2.2.5.2.3 Activation of NK-1 receptors**

Sustained activation of the NMDA receptors causes an increased release of the peptide neurotransmitter substance P in the nociceptors, which binds to neurokinin-1 (NK-1) receptors in the spinal cord. As a result, NK-1 receptors increase pain perception and stimulate nerve growth and regeneration. When substance P binds to NK-1 receptors, the production of the c-Fos oncogene protein is stimulated. The presence of c-Fos protein in spinal cord cells is a marker for central hypersensitisation. The c-Fos protein spreads progressively to higher centres in the spinal cord and can attain the thalamus, resulting in general pain and emotional consequences (Brookoff 2000, 2006).

## Acute versus chronic pain



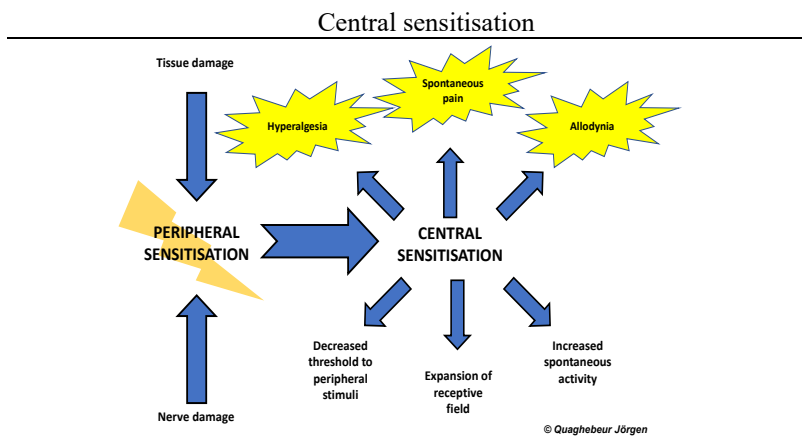
NMDA: N-methyl-D-aspartate; AMPA: Alpha-amino-3-hydroxy-5-methyl-isoxazole-4 propionic acid; NK: neurokinin; PKC: protein kinase C; NO: nitric oxide (Brookoff 2000, 2006)

**Figure 2.14: Summary of mechanisms in acute versus chronic pain**

Neurons can transmit signals in the afferent or efferent direction because of the orthodrome, and antidromically transport within the cell. Chronic pain and plasticity of the nervous system can cause the dorsal horn to release mediators (e.g. nerve growth factor, substance P) that cause action potentials to fire antidromically, and the inflammatory pain mediators NGF and substance P are released at the peripheral nerve endings. NGF increases the excitability of the nociceptors (Brookoff 2000, 2006). Figure 2.14 shows the physiologic aspects of acute and chronic pain.

### 2.2.5.3 Step 3: peripheral and central sensitisation

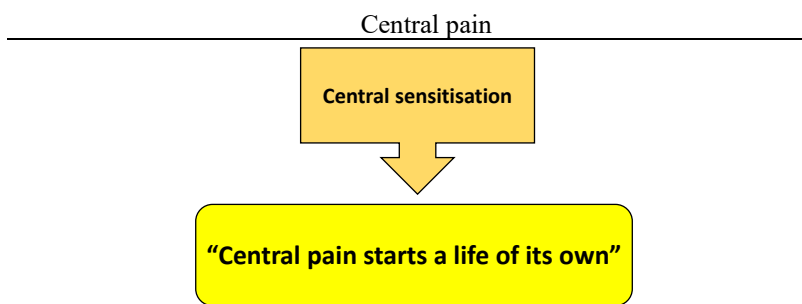
Tissue or nerve damage can elicit peripheral and central sensitisation, influencing the pain sensation (e.g. hyperalgesia, allodynia, spontaneous pain). Figure 2.15 shows step 3 of the chronic pain process.



**Figure 2.15: Step 3 from peripheral to central sensitisation**

Hypersensitivity towards somatic stimuli suggests an alteration of central mechanisms in the processing of sensory events from the bladder (Ness et al. 2005).

#### 2.2.5.4 Step 4: central sensitisation



**Figure 2.16: Central pain**

Central sensitisation is mediated at multiple levels, as shown in Figures 2.16 and 2.17.