

# Peripheral and Central Mechanisms of Pain Generation

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**Abstract** Pain research has uncovered important neuronal mechanisms that underlie clinically relevant pain states such as inflammatory and neuropathic pain. Importantly, both the peripheral and the central nociceptive system contribute significantly to the generation of pain upon inflammation and nerve injury. Peripheral nociceptors are sensitized during

inflammation, and peripheral nerve fibres develop ectopic discharges upon nerve injury or disease. As a consequence a complex neuronal response is evoked in the spinal cord where neurons become hyperexcitable, and a new balance is set between excitation and inhibition. The spinal processes are significantly influenced by brain stem circuits that inhibit or facilitate spinal nociceptive processing. Numerous mechanisms are involved in peripheral and central nociceptive processes including rapid functional changes of signalling and long-term regulatory changes such as up-regulation of mediator/receptor systems. Conscious pain is generated by thalamocortical networks that produce both sensory discriminative and affective components of the pain response.

**Keywords** Nociceptive system · Nociceptors · Inflammatory pain · Neuropathic pain · Peripheral sensitization · Central sensitization · Ectopic discharges · Descending inhibition · Descending facilitation

## 1

### Introduction on Pain

#### 1.1

##### Types of Pain

In daily life the sensation pain is specifically evoked by potential or actual noxious (i.e. tissue damaging) stimuli applied to the body such as heat, squeezing a skin fold or over-rotating a joint. The predictable correlation between the noxious stimulus and the pain sensation causes us to avoid behaviour and situations that evoke pain. Pain during disease is different from “normal” pain. It occurs in the absence of external noxious stimuli, during mild stimulation or in an unpredictable way. Types of pain have been classified according to their pathogenesis, and pain research intends to define their neuronal mechanisms.

Cervero and Laird (1991) distinguish between three types of pain. Application of an acute noxious stimulus to normal tissue elicits *acute physiological nociceptive pain*. It protects tissue from being (further) damaged because withdrawal reflexes are usually elicited. *Pathophysiological nociceptive pain* occurs when the tissue is inflamed or injured. It may appear as spontaneous pain (pain in the absence of any intentional stimulation) or as hyperalgesia and/or allodynia. Hyperalgesia is extreme pain intensity felt upon noxious stimulation, and allodynia is the sensation of pain elicited by stimuli that are normally below pain threshold. In non-neuropathic pain, some authors include the lowering of the pain threshold in the term hyperalgesia. While nociceptive pain is elicited by stimulation of the sensory endings in the tissue, *pain!neuropathic* results from injury or disease of neurons in the peripheral or central nervous system. It does not primarily signal noxious tissue stimulation and often feels abnormal. Its character is often burning or electrical, and it can be persistent or occur in short episodes (e.g. trigeminal neuralgia). It may be combined with hyperalgesia and allodynia. During allodynia even touching the skin can cause

intense pain. Causes of neuropathic pain are numerous, including axotomy, nerve or plexus damage, metabolic diseases such as diabetes mellitus, or herpes zoster. Damage to central neurons (e.g. in the thalamus) can cause central neuropathic pain.

This relatively simple classification of pain will certainly be modified for several reasons. First, in many cases pain is not strictly inflammatory or neuropathic because neuropathy may involve inflammatory components and neuropathic components may contribute to inflammatory pain states. Second, pain research now addresses other types of pain such as pain during surgery (incisional pain), cancer pain, pain during degenerative diseases (e.g. osteoarthritis), or pain in the course of psychiatric diseases. This research will probably lead to a more diversified classification that takes into account general and disease-specific neuronal mechanisms.

An important aspect is the distinction between acute and chronic pain. Usually pain in patients is called “chronic” when it lasts longer than 6 months (Russo and Brose 1998). Chronic pain may result from a chronic disease and may then actually result from persistent nociceptive processes. More recently the emphasis with chronic pain is being put on its character. In many chronic pain states the causal relationship between nociception and pain is not tight and pain does not reflect tissue damage. Rather psychological and social factors seem to influence the pain, e.g. in many cases of low back pain (Kendall 1999). Chronic pain may be accompanied by neuroendocrine dysregulation, fatigue, dysphoria, and impaired physical and even mental performance (Chapman and Gavrin 1999).

## 1.2

### **The Nociceptive System: An Overview**

Nociception is the encoding and processing of noxious stimuli in the nervous system that can be measured with electrophysiological techniques. Neurons involved in nociception form the nociceptive system. Noxious stimuli activate primary nociceptive neurons with “free nerve endings” (A $\delta$  and C fibres, nociceptors) in the peripheral nerve. Most of the nociceptors respond to noxious mechanical (e.g. squeezing the tissue), thermal (heat or cold), and chemical stimuli and are thus polymodal (cf. in Belmonte and Cervero 1996). Nociceptors can also exert efferent functions in the tissue by releasing neuropeptides [substance P (SP), calcitonin gene-related peptide (CGRP)] from their sensory endings. Thereby they induce vasodilatation, plasma extravasation, attraction of macrophages or degranulation of mast cells, etc. This inflammation is called neurogenic inflammation (Lynn 1996; Schaible et al. 2005).

Nociceptors project to the spinal cord and form synapses with second order neurons in the grey matter of the dorsal horn. A proportion of second-order neurons have ascending axons and project to the brain stem or to the thalamocortical system that produces the conscious pain response upon noxious

stimulation. Other spinal cord neurons are involved in nociceptive motor reflexes, more complex motor behaviour such as avoidance of movements, and the generation of autonomic reflexes that are elicited by noxious stimuli.

Descending tracts reduce or facilitate the spinal nociceptive processing. The descending tracts are formed by pathways that originate from brainstem nuclei (in particular the periaqueductal grey, the rostral ventromedial medulla) and descend in the dorsolateral funiculus of the spinal cord. Descending inhibition is part of an intrinsic antinociceptive system (Fields and Basbaum 1999).

## 2

### **The Peripheral Pain System: Primary Afferent Nociceptors**

#### 2.1

##### **Responses to Noxious Stimulation of Normal Tissue**

Nociceptors of different tissues are assumed to share most of their general properties. However, qualitative and quantitative differences of neurons supplying different tissues cannot be ruled out, e.g. the mechanical threshold of nociceptors may be quite different in different tissues because the potentially damaging stimuli may be of low (as in the cornea) or higher intensity (in the skin, muscle or joint). Furthermore, evidence was provided that dorsal root ganglion (DRG) neurons supplying fibres to different tissues differ in their passive and active electrophysiological properties (Gold and Traub 2004). Thus, subtle differences in nociceptor properties may be important for pain mechanisms in different tissues.

In skin, muscle and joint, many A $\delta$  and C fibres have elevated thresholds for mechanical stimuli, thus acting as specific nociceptors that detect potentially or actually damaging mechanical stimuli. At least in the skin many nociceptors respond to noxious heat. The heat threshold may be below the frankly noxious range but the neurons encode different heat intensities by their response frequency. In some visceral organs such as the bladder, most slow-conducting fibres have thresholds in the innocuous range and stronger responses in the noxious range, raising the possibility that visceral noxious stimuli are also encoded by “wide dynamic range neurons” and not only by specific nociceptors. In addition, many nociceptors are sensitive to chemical stimuli (chemosensitivity). Most of the nociceptors are thus polymodal (cf. Belmonte and Cervero).

Nociceptors are different from afferents subserving other modalities. Most fast-conducting A $\beta$  afferents with corpuscular endings are mechano-receptors that respond vigorously to innocuous mechanical stimuli. Although they may show their strongest response to a noxious stimulus, their discharge pattern does not discriminate innocuous from noxious stimuli. A proportion of A $\delta$  and C fibres are warmth or cold receptors encoding innocuous warm and cold stimuli but not noxious heat and cold.

In addition to polymodal nociceptors, joint, skin and visceral nerves contain A $\delta$  and C fibres that were named silent or initially mechano-insensitive nociceptors. These neurons are not activated by noxious mechanical and thermal stimuli in normal tissue. However, they are sensitized during inflammation and then start to respond to mechanical and thermal stimuli (Schaible and Schmidt 1988; Weidner et al. 1999). In humans this class of nociceptors exhibits a particular long-lasting response to algogenic chemicals, and such nociceptors are crucial in mediating neurogenic inflammation (Ringkamp et al. 2001). Moreover, they play a major role in initiating central sensitization (Kleede et al. 2003). These neurons have distinct axonal biophysical characteristics separating them from polymodal nociceptors (Orstavik et al. 2003; Weidner et al. 1999).

## 2.2

### **Changes of Neuronal Responses During Inflammation (Peripheral Sensitization)**

During inflammation the excitation threshold of polymodal nociceptors drops such that even normally innocuous, light stimuli activate them. Noxious stimuli evoke stronger responses than in the non-sensitized state. After sensitization of “pain fibres”, normally non-painful stimuli can cause pain. Cutaneous nociceptors are in particular sensitized to thermal stimuli; nociceptors in deep somatic tissue such as joint and muscle show pronounced sensitization to mechanical stimuli (Campbell and Meyer 2005; Mense 1993; Schaible and Grubb 1993). In addition, during inflammation initially mechano-insensitive nerve fibres become mechano-sensitive. This recruitment of silent nociceptors adds significantly to the inflammatory nociceptive input to the spinal cord. Resting discharges may be induced or increased in nociceptors because of inflammation, providing a continuous afferent barrage into the spinal cord.

## 2.3

### **Peripheral Neuronal Mechanisms of Neuropathic Pain**

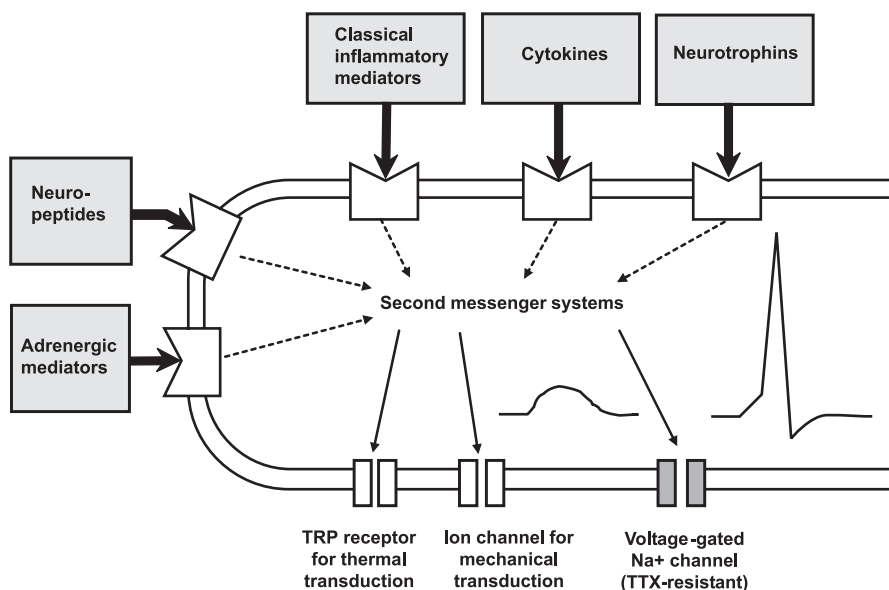
In healthy sensory nerve fibres action potentials are generated in the sensory endings upon stimulation of the receptive field. Impaired nerve fibres often show pathological ectopic discharges. These action potentials are generated at the site of nerve injury or in the cell body in DRG. The discharge patterns vary from rhythmic firing to intermittent bursts (Han et al. 2000; Liu et al. 2000). Ectopic discharges occur in A $\delta$  and C fibres and in thick myelinated A $\beta$  fibres. Thus, after nerve injury both low threshold A $\beta$  as well as high threshold A $\delta$  and C fibres may be involved in the generation of pain. A $\beta$  fibres may evoke exaggerated responses in spinal cord neurons that have undergone the process of central sensitization (see Sect. 3.3.2). Recently, however, it was proposed that pain is not generated by the injured nerve fibres themselves but rather by intact

nerve fibres in the vicinity of injured nerve fibres. After an experimental lesion in the L5 dorsal root, spontaneous action potential discharges were observed in C fibres in the uninjured L4 dorsal root. These fibres may be affected by the process of a Wallerian degeneration (Wu et al. 2001).

## 2.4

### Molecular Mechanisms of Activation and Sensitization of Nociceptors

Recent years have witnessed considerable progress in the understanding of molecular events that lead to activation and sensitization of nociceptors. Nociceptors express ion channels for stimulus transduction and action potential generation, and a large number of receptors for inflammatory and other mediators (Fig. 1). These receptors are either coupled to ion channels or, more often, activate second messenger systems that influence ion channels. Sensitization of nociceptors by inflammatory mediators is induced within a few minutes. If noxious stimuli or inflammatory conditions persist, the expression of ion channels, receptors and mediator substances may change. An up-regulation of excitatory receptors may contribute to the maintenance of pain. Furthermore, some receptors exert trophic influences on the neurons regulating synthesis of mediators and expression of ion channels and receptors in these cells.



**Fig. 1** Model of the sensory ending of a nociceptor showing ion channels for transduction of thermal and mechanical stimuli and action potential generation and metabotropic receptors subserving chemosensitivity

### 2.4.1

#### TRP Channels

The first cloned nociceptive ion channel was the TRPV1 receptor, which is expressed in about 40% of DRG cells. This ion channel is opened by binding of capsaicin, the compound in hot pepper that causes burning pain. In particular,  $\text{Ca}^{2+}$  flows through this channel and depolarizes the cell. The TRPV1 receptor is considered one of the transducers of noxious heat because it is opened by heat ( $>43^\circ\text{C}$ ). In TRPV1 knock-out mice, the heat response is not abolished but the mice do not exhibit thermal hyperalgesia during inflammation, showing the importance of TRPV1 for inflammatory hyperalgesia (Caterina et al. 2000; Davis et al. 2000). Up-regulation of TRPV1 transcription during inflammation explains longer-lasting heat hypersensitivity (Ji et al. 2002; Wilson-Gering et al. 2005). Following experimental nerve injury and in animal models of diabetic neuropathy, TRPV1 receptor is present on neurons that do not normally express TRPV1 (Rashid et al. 2003; Hong and Wiley 2005).

The TRPV1 receptor is a member of the TRP (transient receptor protein) family. Other TRP members may be transducers of temperature stimuli in other ranges (Papapoutian et al. 2003). The TRPV2 receptor in nociceptors is thought to be a transducer for extreme heat (threshold  $>50^\circ\text{C}$ ). TRPA1 could be the transducer molecule in nociceptors responding to cold (Peier et al. 2002). It is activated by pungent compounds, e.g. those present in cinnamon oil, mustard oil and ginger (Bandell et al. 2004). By contrast, TRPV3 and/or TRPV4 may be transduction molecules for innocuous warmth in warm receptors, and TRPM8 may transduce cold stimuli in innocuous cold receptors. Although the putative warmth transducer TRPV4 shows some mechano-sensitivity, it is still unclear whether TRPV4 is involved in the transduction of mechanical stimuli (Marchand et al. 2005).

### 2.4.2

#### Voltage-Gated Sodium Channels and ASICs

While most voltage-gated  $\text{Na}^+$  channels are blocked by tetrodotoxin (TTX), many small DRG cells express TTX-resistant (R)  $\text{Na}^+$  channels ( $\text{Na}_V1.8$  and  $\text{Na}_V1.9$ ) in addition to TTX-sensitive (S)  $\text{Na}^+$  channels. Both TTX-S and TTX-R  $\text{Na}^+$  channels contribute to the  $\text{Na}^+$  influx during the action potential. Interestingly, TTX-R  $\text{Na}^+$  currents are influenced by inflammatory mediators. They are enhanced e.g. by prostaglandin  $\text{E}_2$  ( $\text{PGE}_2$ ) that sensitizes nociceptors (McCleskey and Gold 1999). This raises the possibility that TTX-R  $\text{Na}^+$  channels also play a role in the transduction process of noxious stimuli (Brock et al. 1998).  $\text{SNS}^-/-$  knock-out mice (SNS is a TTX-R  $\text{Na}^+$  channel) exhibit pronounced mechanical hypoalgesia but only small deficits in the response to thermal stimuli (Akopian et al. 1999).

Acid sensing ion channels (ASICs) are  $\text{Na}^+$  channels that are opened by low pH. This is of interest because many inflammatory exudates exhibit a low pH. Protons directly activate ASICs with subsequent generation of action potentials (Sutherland et al. 2001).

### 2.4.3

#### **Receptors of Inflammatory Mediators (Chemosensitivity of Nociceptors)**

The chemosensitivity of nociceptors allows inflammatory and trophic mediators to act on these neurons. Sources of inflammatory mediators are inflammatory cells and non-neuronal tissue cells. The field of chemosensitivity is extremely complicated due to the large numbers of receptors that have been identified in primary afferent neurons (Gold 2005; Marchand et al. 2005). Receptors that are involved in the activation and sensitization of neurons are either ionotropic (the mediator opens an ion channel) or metabotropic (the mediator activates a second messenger cascade that influences ion channels and other cell functions). Many receptors are coupled to G proteins, which signal via the production of the second messengers cyclic AMP (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol and phospholipase C. Other receptor subgroups include receptors bearing intrinsic protein tyrosine kinase domains, receptors that associate with cytosolic tyrosine kinases and protein serine/threonine kinases (Gold 2005). Table 1 shows the mediators to which receptors are expressed in sensory neurons (Gold 2005; Marchand et al. 2005). It is beyond the scope of this chapter to describe all the important mediators. Many of the mediators and their receptors will be addressed in the following chapters.

Functions of mediators are several-fold. Some of them activate neurons directly (e.g. the application of bradykinin evokes action potentials by itself) and/or they sensitize neurons for mechanical, thermal and chemical stimuli (e.g. bradykinin and prostaglandins increase the excitability of neurons so that mechanical stimuli evoke action potentials at a lower threshold than under control conditions).  $\text{PGE}_2$ , for example, activates G protein-coupled EP receptors that cause an increase of cellular cAMP. This second messenger activates protein kinase A, and this pathway influences ion channels in the membrane, leading to an enhanced excitability of the neuron with lowered threshold and increased action potential frequency elicited during suprathreshold stimulation. Bradykinin receptors are of great interest because bradykinin activates numerous A $\delta$  and C fibres and sensitizes them for mechanical and thermal stimuli (Liang et al. 2001). Bradykinin receptor antagonists reverse thermal hyperalgesia, and Freund's complete adjuvant induced mechanical hyperalgesia of the rat knee joints. Some reports suggest that in particular bradykinin B1 receptors are up-regulated in sensory neurons following tissue or nerve injury, and that B1 antagonists reduce hyperalgesia. Other authors also found an up-regulation of B2 receptors during inflammation (Banik et al. 2001; Segond von Banchet et al. 2000).



**Table 1** Receptors in subgroups of sensory neurons**Ionotropic receptors for**

ATP, H<sup>+</sup> (acid-sensitive ion channels, ASICs), glutamate (AMPA, kainate, NMDA receptors), acetylcholine (nicotinic receptors), serotonin (5-HT<sub>3</sub>)

**Metabotropic receptors for**

Acetylcholine, adrenaline, serotonin, dopamine, glutamate, GABA, ATP  
 Prostanoids (prostaglandin E<sub>2</sub> and I<sub>2</sub>), bradykinin, histamine, adenosine, endothelin  
 Neuropeptides (e.g. substance P, calcitonin gene-related peptide, somatostatin, opioids)  
 Proteases (protease-activated receptors, PAR1 and PAR2)  
 Neurotrophins [tyrosine kinase (Trk) receptors]  
 Glial cell line-derived neurotrophic factor (GDNF)  
 Inflammatory cytokines (non-tyrosine kinase receptors)

While prostaglandins and bradykinin are “classical” inflammatory mediators, the list of important mediators will be extended by cytokines. Some cytokines such as interleukin (IL)-1 $\beta$  are pro-nociceptive upon application to the tissue (Obreja et al. 2003). It is likely that cytokines play an important role in both inflammatory and neuropathic pain (Marchand et al. 2005; Sommer and Schröder 1995).

Neurotrophins are survival factors during the development of the nervous system, but during inflammation of the tissue, the level of nerve growth factor (NGF) is substantially enhanced. By acting on the tyrosine kinase A (trk A) receptors, NGF increases the synthesis of SP and CGRP in the primary afferents. NGF may also act on mast cells and thereby activate and sensitize sensory endings by mast cell degranulation (cf. Schaible and Richter 2004).

**2.4.4****Neuropeptide Receptors and Adrenergic Receptors**

Receptors for several neuropeptides have been identified in primary afferent neurons, including receptors for the excitatory neuropeptides SP (neurokinin 1 receptors) and CGRP, and receptors for inhibitory peptides, namely for opioids, somatostatin and neuropeptide Y (NPY) (for review see Bär et al. 2004; Brack and Stein 2004). These receptors could be autoreceptors because some of the neurons with these receptors also synthesize the corresponding neuropeptide. It has been proposed that the activity or threshold of a neuron results from the balance between excitatory and inhibitory compounds. Many nociceptive neurons, for example, seem to be under the tonic inhibitory influence of somatostatin because the application of a somatostatin receptor antagonist enhances activation of the neurons by stimuli (Carlton et al. 2001; Heppelmann

and Pawlak 1999). The expression of excitatory neuropeptide receptors in the neurons can be increased under inflammatory conditions (Carlton et al. 2002; Segond von Banchet et al. 2000).

The normal afferent fibre does not seem to be influenced by stimulation of the sympathetic nervous system. However, primary afferents from inflamed tissue may be activated by sympathetic nerve stimulation. The expression of adrenergic receptors may be particularly important in neuropathic pain states (see the following section).

## 2.5

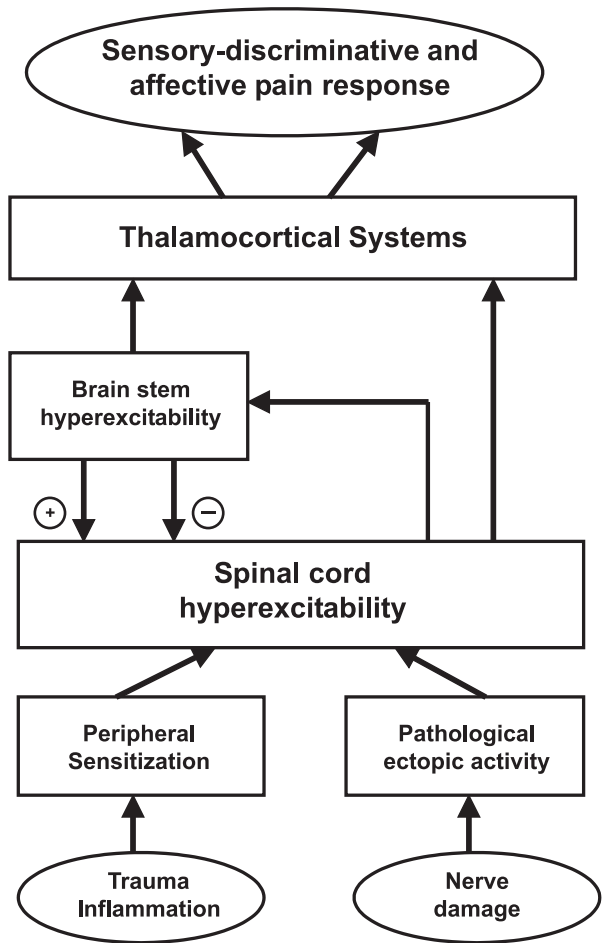
### **Mechanisms Involved in the Generation of Ectopic Discharges After Nerve Injury**

Different mechanisms may produce ectopic discharges. After nerve injury the expression of TTX-S  $\text{Na}^+$  channels is increased, and the expression of TTX-R  $\text{Na}^+$  channels is decreased. These changes are thought to alter the membrane properties of neurons such that rapid firing rates (bursting ectopic discharges) are favoured (Cummins et al. 2000). Changes in the expression of potassium channels of the neurons have also been shown (Everill et al. 1999). Injured axons may be excited by inflammatory mediators, e.g. by bradykinin, NO (Michaelis et al. 1998) and cytokines (Cunha and Ferreira 2003; Marchand et al. 2005). Sources of these mediators are white blood cells and Schwann cells around the damaged nerve fibres. Finally, the sympathetic nervous system does not activate primary afferents in normal tissue, but injured nerve fibres may become sensitive to adrenergic mediators (Kingerly et al. 2000; Lee et al. 1999; Moon et al. 1999). This cross-talk may occur at different sites. Adrenergic receptors may be expressed at the sensory nerve fibre ending. Direct connections between afferent and efferent fibres (so-called “ephapses”) is considered. Sympathetic endings are expressed in increased numbers in the spinal ganglion after nerve injury, and cell bodies of injured nerve fibres are surrounded by “baskets” consisting of sympathetic fibres (Jänig et al. 1996).

## 3

### **Spinal Nociceptive Processing**

The spinal cord is the lowest level of the central nociceptive system. The neuronal organization of the spinal cord determines characteristic features of pain, e.g. the projection of pain into particular tissues. The spinal cord actively amplifies the spinal nociceptive processing because nociceptive spinal cord neurons change their excitability to inputs from the periphery under painful conditions. On the other hand the spinal cord is under the influence of descending influences. Figure 2 shows functionally important aspects of the nociceptive processing in the central nervous system.



**Fig. 2** Schematic display of the nociceptive processing underlying inflammatory and neuropathic pain

**3.1**  
**Types of Nociceptive Spinal Neurons and Responses to Noxious Stimulation of Normal Tissue**

Nociceptive A $\delta$  fibres project mainly to lamina I (and II). Some A $\delta$  fibres have further projections into lamina V. Cutaneous C fibres project mainly to lamina II, but visceral and muscular unmyelinated afferents project to lamina II and also to deeper laminae. Visceral afferents distribute to a wider area of the cord, but the number of terminals for each fibre is much lower for visceral than for cutaneous fibres (Sugiura et al. 1989). By contrast, non-nociceptive primary afferents with A $\beta$  fibres project to lamina III and IV. However, not

only neurons in the superficial dorsal horn receive direct inputs from primary afferent neurons; dendrites of deep dorsal horn may extend dorsally into the superficial laminae and receive nociceptive inputs in superficial layers (Willis and Coggeshall 2004).

Neurons with nociceptive response properties are located in the superficial and deep dorsal and in the ventral horn. Both wide dynamic range neurons and nociceptive-specific neurons encode the intensity of a noxious stimulus applied to a specific site. Wide dynamic range neurons receive inputs from A $\beta$ , A $\delta$  and C fibres and respond in a graded fashion to innocuous and noxious stimulus intensities. Nociceptive-specific neurons respond only to A $\delta$  and C fibre stimulation and noxious stimulus intensities.

A proportion of neurons receive only inputs from the skin or from deep tissue such as muscle and joint. However, many neurons exhibit convergent inputs from skin and deep tissue, and all neurons that receive inputs from the viscera also receive inputs from skin (and deep tissue). This uncertainty in the message of a neuron could in fact be the reason why, during disease in viscera, pain is felt as occurring in a cutaneous or subcutaneous area; the pain is projected into a so-called Head zone. Another encoding problem is that, in particular, wide dynamic range neurons often have large receptive fields, and a stimulus of a defined intensity may elicit different intensities of responses when applied to different sites of the receptive field. Quite clearly, the precise location of a noxious stimulus, its intensity and character cannot be encoded by a single nociceptive neuron. Presumably, encoding of a noxious stimulus is only achieved by a population of nociceptive neurons (see Price et al. 2003). By contrast, other authors propose that only lamina I neurons with smaller receptive fields are able to encode noxious stimuli, thus forming labelled lines from spinal cord to the cortex (for review see Craig 2003).

The response of a spinal cord neuron is dependent on its primary afferent input, its spinal connections and on descending influences. Evidence has been provided that loops of neurons involving the brain stem influence the responses of nociceptive neurons. These loops may mainly originate in neurons in projection neurons in lamina I (see the following section) and facilitate, via descending fibres from the brain stem, neurons in superficial and deep dorsal horn (Suzuki et al. 2002). In addition, descending inhibition influences responses of neurons (see Sect. 4.1).

Samples of activated neurons can be mapped by visualizing FOS protein in neurons (Willis and Coggeshall 2004). Noxious heat stimulation, for example, evokes expression of C-FOS within a few minutes in the superficial dorsal horn, and causes staining shifts to deeper laminae of the dorsal horn thereafter (Menetr y et al. 1989; Williams et al. 1990). Noxious visceral stimulation evokes C-FOS expression in laminae I, V and X, thus resembling the projection area of visceral afferent fibres, and injection of mustard oil into the muscle elicited C-FOS expression in laminae I and IV to VI (Hunt et al. 1987; Menetr y et al. 1989).

### 3.2

#### **Projections of Nociceptive Spinal Cord Neurons to Supraspinal Sites**

The axons of most dorsal horn neurons terminate in the same or adjacent laminae, i.e. they are local interneurons. However, a proportion of neurons projects to supraspinal sites. Ascending pathways in the white matter of the ventral quadrant of the spinal cord include the spinothalamic tract (STT), the spinoreticular tract (SRT), and the spinomesencephalic tract (SMT). Axons of the STT originate from neurons in lamina I (some lamina I STT cells may ascend in the dorsolateral funiculus), lamina V and deeper. Many STT cells project to the thalamic ventral posterior lateral (VPL) nucleus, which is part of the lateral thalamocortical system and is involved in encoding of sensory stimuli (see Sect. 5). Some STT cells project to thalamic nuclei that are not involved in stimulus encoding, and they have collaterals to the brain stem. Axons of the SRT project to the medial rhombencephalic reticular formation, the lateral and dorsal reticular nucleus, the nucleus reticularis gigantocellularis and others. SRT cells are located in laminae V, VII, VIII and X, and they have prominent responses to deep input. SMT neurons are located in laminae I, IV, V, VII and VIII and project to the parabrachial nuclei and the periaqueductal grey and others. The parabrachial projection reaches in part to neurons that project to the central nucleus of amygdala. STT, SRT and SMT cells are either low-threshold, wide dynamic range or nociceptive-specific.

In addition, several spinal projection paths have direct access to the limbic system, namely the spinohypothalamic tract, the spino-parabrachio-amygdalar pathway, the spino-amygdalar pathway and others. In some species there is a strong spino-cervical tract (SCT) ascending in the dorsolateral funiculus. SCT neurons process mainly mechano-sensory input, but some additionally receive nociceptive inputs (Willis and Coggeshall 2004). Finally, there is substantial evidence that nociceptive input from the viscera is processed in neurons that ascend in the dorsal columns (Willis 2005).

### 3.3

#### **Plasticity of Nociceptive Processing in the Spinal Cord**

Importantly, spinal cord neurons show changes of their response properties including the size of their receptive fields when the peripheral tissue is sufficiently activated by noxious stimuli, when thin fibres in a nerve are electrically stimulated, or when nerve fibres are damaged. In addition descending influences contribute to spinal nociceptive processing (see Sect. 4 and Fig. 2). In general it is thought that plasticity in the spinal cord contributes significantly to clinically relevant pain states.

### 3.3.1

#### **Wind-Up, Long-Term Potentiation and Long-Term Depression**

Wind-up is a short-term increase of responses of a spinal cord neuron when electrical stimulation of afferent C fibres is repeated at intervals of about 1 s (Mendell and Wall 1965). The basis of wind-up is a prolonged excitatory post-synaptic potential (EPSP) in the dorsal horn neuron that builds up because of a repetitive C fibre volley (Sivilotti et al. 1993). Wind-up disappears quickly when repetitive stimulation is stopped. It produces a short-lasting increase of responses to repetitive painful stimulation. Neurons may also show wind-down.

Long-term potentiation (LTP) and long-term depression (LTD) are long-lasting changes of synaptic activity after peripheral nerve stimulation (Randic et al. 1993; Rygh et al. 1999; Sandkühler and Liu 1998). LTP can be elicited at a short latency after application of a high-frequency train of electrical stimuli that are suprathreshold for C fibres, in particular when descending inhibitory influences are interrupted. However, LTP can also be elicited with natural noxious stimulation, although the time course is much slower (Rygh et al. 1999). By contrast, LTD in the superficial dorsal horn is elicited by electrical stimulation of A $\delta$  fibres. It may be a basis of inhibitory mechanisms that counteract responses to noxious stimulation (Sandkühler et al. 1997).

### 3.3.2

#### **Central Sensitization (Spinal Hyperexcitability)**

In the course of inflammation and nerve damage neurons in the superficial, the deep and the ventral cord show pronounced changes of their response properties, a so-called central sensitization. This form of neuroplasticity has been observed during cutaneous inflammation, after cutaneous capsaicin application and during inflammation in joint, muscle and viscera. Typical changes of responses of individual neurons are:

- Increased responses to noxious stimulation of inflamed tissue.
- Lowering of threshold of nociceptive specific spinal cord neurons (they change into wide dynamic range neurons).
- Increased responses to stimuli applied to non-inflamed tissue surrounding the inflamed site.
- Expansion of the receptive field.

In particular, the enhanced responses to stimuli applied to non-inflamed tissue around the inflamed zone indicate that the sensitivity of the spinal cord neurons is enhanced so that a previously subthreshold input is sufficient to

activate the neuron. After sensitization, an increased percentage of neurons in a segment respond to stimulation of an inflamed tissue. Central sensitization can persist for weeks, judging from the recording of neurons at different stages of acute and chronic inflammation (for review see Dubner and Ruda 1992; Mense 1993; Schaible and Grubb 1993).

Evidence for central sensitization has been observed in neuropathic pain states in which conduction in the nerve remains present and thus a receptive field of neurons can be identified. In these models more neurons show ongoing discharges and, on average, higher responses can be elicited by innocuous stimulation of receptive fields (Laird and Bennett 1993; Palacek et al. 1992a, b). In some models of neuropathy neurons with abnormal discharge properties can be observed.

During inflammation and neuropathy a large number of spinal cord neurons express C-FOS, supporting the finding that a large population of neurons is activated. At least at some time points metabolism in the spinal cord is enhanced during inflammation and neuropathy (Price et al. 1991; Schadrack et al. 1999).

The mechanisms of central sensitization are complex, and it is likely that different pain states are characterized at least in part by specific mechanisms, although some of the mechanisms are involved in all types of central sensitization. It may be crucial whether central sensitization is induced by increased inputs in sensitized but otherwise normal fibres (such as in inflammation), or whether structural changes such as neuronal loss contribute (discussed for neuropathic pain, see Campbell and Meyer 2005). Mechanisms of central sensitization are discussed in Sect. 3.5.

### 3.4

#### **Synaptic Transmission of Nociceptive Input in the Dorsal Horn**

Numerous transmitters and receptors mediate the processing of noxious information arising from noxious stimulation of normal tissue, and they are involved in plastic changes of spinal cord neuronal responses during peripheral inflammation and nerve damage (see Sect. 3.5). Transmitter actions have either fast kinetics (e.g. action of glutamate and ATP at ionotropic receptors) or slower kinetics (in particular neuropeptides that act through G protein-coupled metabotropic receptors). Actions at fast kinetics evoke immediate and short effects on neurons, thus encoding the input to the neuron, whereas actions at slow kinetics modulate synaptic processing (Millan 1999; Willis and Coggeshall 2004).

Glutamate is a principal transmitter of primary afferent and dorsal horn neurons. It activates ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate [non-*N*-methyl-D-aspartate (NMDA)] and NMDA receptors. In particular in the substantia gelatinosa, evoked synaptic activity is mainly blocked by antagonists at non-NMDA receptors whereas

NMDA receptor antagonists usually cause a small reduction of mainly later EPSP components. Both non-NMDA and NMDA receptors are involved in the synaptic activation of neurons by noxious stimuli (cf. Fundytus 2001; Millan 1999; Willis and Coggeshall 2004). ATP has been implicated in synaptic transmission of innocuous mechano-receptive and nociceptive input in the superficial dorsal horn. Purinergic ATP receptors are expressed in dorsal horn neurons and in DRG cells, mediating enhanced release of glutamate (cf. Willis and Coggeshall 2004).

Excitatory neuropeptides are co-localized with glutamate. Neuropeptide-mediated EPSPs usually occur after a latency of seconds and are long-lasting. They may not be sufficient to evoke action potential generation but act synergistically with glutamate (Urban et al. 1994). SP is released mainly in the superficial dorsal horn by electrical stimulation of unmyelinated fibres and during noxious mechanical, thermal or chemical stimulation of the skin and deep tissue. Neurokinin-1 (NK-1) receptors for SP are mainly located on dendrites and cell bodies of dorsal horn neurons in laminae I, IV–VI and X. Upon strong activation by SP, NK-1 receptors are internalized. Mice with a deletion of the preprotachykinin A have intact responses to mildly noxious stimuli but reduced responses to moderate and intense noxious stimuli. Mice with a deleted gene for the production of NK-1 receptors respond to acutely painful stimuli but lack intensity coding for pain and wind-up. In addition, neurokinin A (NKA) is found in small DRG cells and in the dorsal horn and spinally released upon noxious stimulation. CGRP is often colocalized with substance P in DRG neurons. It is spinally released by electrical stimulation of thin fibres and noxious mechanical and thermal stimulation. CGRP binding sites are located in lamina I and in the deep dorsal horn. CGRP enhances actions of SP by inhibiting its enzymatic degradation and potentiating its release. CGRP activates nociceptive dorsal horn neurons; blockade of CGRP effects reduces nociceptive responses. Other excitatory neuropeptides in the dorsal horn are vasoactive intestinal polypeptide (VIP), neurotensin, cholecystokinin (CCK, antinociceptive effects of CCK have also been described), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH) and pituitary adenylate cyclase-activating polypeptide (PACAP) (for review see Willis and Coggeshall 2004).

$\gamma$ -Aminobutyric acid (GABA)ergic inhibitory neurons are located throughout the spinal cord. They can be synaptically activated by primary afferent fibres. Both the ionotropic GABA<sub>A</sub> and the metabotropic GABA<sub>B</sub> receptor are located pre-synaptically on primary afferent neurons or post-synaptically on dorsal horn neurons. Responses to both innocuous mechanical and noxious stimuli can be reduced by GABA receptor agonists. Some of the inhibitory effects are due to glycine, and the ventral and the dorsal horn contain numerous glycinergic neurons. Glycine may be co-localized with GABA in synaptic terminals. Many DRG neurons and neurons in the dorsal horn express nicotinic and muscarinic receptors for acetylcholine. Application of acetylcholine to



the spinal cord produces pro- or anti-nociception (cf. Willis and Coggeshall 2004).

The dorsal horn contains leu-enkephalin, met-enkephalin, dynorphin and endomorphins 1 and 2. Enkephalin-containing neurons are particularly located in laminae I and II, with dynorphin-containing neurons in laminae I, II and V. Endomorphin 2 has been visualized in terminals of primary afferent neurons in the superficial dorsal horn and in DRG, but also in post-synaptic neurons. Opiate receptors

( $\mu$ ,  $\delta$ ,  $\kappa$ ) are concentrated in the superficial dorsal horn, and in particular  $\mu$  and  $\delta$  receptors are located in interneurons and on primary afferent fibres. Opioids reduce release of mediators from primary afferents (pre-synaptic effect), responses of neurons to (innocuous and) noxious stimulation and responses to ionophoretic application of excitatory amino acids showing post-synaptic effects of opioids (many dorsal horn neurons are hyperpolarized by opiates). In addition to these "classical" opiate receptors, nociceptin [orphanin fluoroquinolone (FQ)] receptors have been discovered. Nociceptin has similar cellular actions as classical opioid peptides. However, pro-nociceptive effects have also been described. A related peptide is nocistatin. At present it is unknown at which receptor nocistatin acts. Somatostatin is expressed in primary afferent neurons, dorsal horn interneurons and axons that descend from the medulla. It is released mainly in the substantia gelatinosa, by heat stimulation. It is an intriguing question whether inhibitory somatostatin is released in the spinal cord from primary afferent fibres or from interneurons. Galanin is expressed in a subpopulation of small DRG neurons, and galanin binding sites are also expressed on DRG neurons. Both facilitatory and inhibitory effects of galanin have been described in inflammatory and neuropathic pain states. NPY is normally only expressed at very low levels in DRG neurons, but DRG neurons express Y1 and Y2 receptors. It was proposed that Y1 and Y2 receptors contribute to pre-synaptic inhibition (for review see Willis and Coggeshall 2004).

Spinal processing is influenced by numerous other mediators including spinal prostaglandins, cytokines and neurotrophins. These mediators are produced in neurons and/or glia cells (Marchand et al. 2005; Vanegas and Schaible 2001). They are particularly important under pathophysiological conditions (see the following section). In addition, synaptic transmission is influenced by transmitters of descending systems (see Sect. 4.1).

Transmitter release is dependent on  $\text{Ca}^{2+}$ -influx into the pre-synaptic ending through voltage-dependent calcium channels. In addition,  $\text{Ca}^{2+}$  regulates neuronal excitability. Important for the nociceptive processing are high-voltage activated N-type channels, which are mainly located pre-synaptically but also on the post-synaptic side, and P/Q-type channels that are located on the pre-synaptic site. Blockers of N-type channels reduce responses of spinal cord neurons and behavioural responses to noxious stimulation of normal and inflamed tissue, and they reduce neuropathic pain. P/Q-type channels are mainly

involved in the generation of pathophysiological pain states. A role for high-voltage activated L-type channels and low-voltage activated T-type channels has also been discussed (Vanegas and Schaible 2000).

### 3.5

#### **Molecular Events Involved in Spinal Hyperexcitability (Central Sensitization)**

A complex pattern of events takes place in the spinal cord that changes sensitivity of spinal nociceptive processing involving pre- and post-synaptic mechanisms. (1) During peripheral inflammation the spinal release of mediators such as glutamate, SP, neurokinin A and CGRP from nociceptors is increased (Schaible 2005). (2) Spinal cord neurons are sensitized by activation of NMDA receptors, and this process is supported by activation of metabotropic glutamate, NK-1 and CGRP receptors, and brain-derived neurotrophic factor plays a role as well (Woolf and Salter 2000). Antagonists to the NMDA receptor can prevent central sensitization and reduce established hyperexcitability (Fundytus 2001). Antagonists at NK-1 and CGRP receptors attenuate central sensitization. Ablation of neurons with NK-1 receptors was shown to abolish central sensitization (Khasabov et al. 2002). Important molecular steps of sensitization are initiated by  $\text{Ca}^{2+}$  influx into cells through NMDA receptors and voltage-gated calcium channels (Woolf and Salter 2000).  $\text{Ca}^{2+}$  activates  $\text{Ca}^{2+}$ -dependent kinases that e.g. phosphorylate NMDA receptors. (3) The subunits NR1 and GluR1 of glutamate receptors show an up-regulation of the protein and an increase of phosphorylation (also of the NR2B NMDA receptor subunit) thus enhancing synaptic glutamatergic transmission. First changes appear within 10 min after induction of inflammation and correlate well with behavioural hyperalgesia (Dubner 2005). (4) Expression of genes that code for neuropeptides is enhanced. In particular, increased gene expression of opioid peptides (dynorphin and enkephalin) have become known, suggesting that inhibitory mechanisms are up-regulated for compensation. However, dynorphin has both an inhibitory action via  $\kappa$  receptors and excitatory actions involving NMDA receptors. (5) Other mediators such as spinal prostaglandins and cytokines modify central hyperexcitability. As mentioned above, sources of these mediators are neurons, glia cells, or both (Marchand et al. 2005; Watkins and Maier 2005). Spinal actions of prostaglandins include increase of transmitter release (cf. Vanegas and Schaible 2001), inhibition of glycinergic inhibition (Ahmadi et al. 2002) and direct depolarization of dorsal horn neurons (Baba et al. 2001).

In the case of neuropathic pain, loss of inhibition is being discussed as a major mechanism of spinal hyperexcitability. Reduced inhibition may be produced by loss of inhibitory interneurons through excitotoxic actions and apoptosis (Dubner 2005, see, however, Polgár et al. 2004).

## 4

### **Descending Inhibition and Facilitation**

#### 4.1

##### **Periaqueductal Grey and Related Brain Stem Nuclei**

From brain stem nuclei, impulses “descend” onto the spinal cord and influence the transmission of pain signals at the dorsal horn (cf. Fields and Basbaum 1999; Ossipov and Porreca 2005). Concerning descending inhibition, the periaqueductal grey matter (PAG) is a key region. It projects to the rostral ventromedial medulla (RVM), which includes the serotonin-rich nucleus raphe magnus (NRM) as well as the nucleus reticularis gigantocellularis pars alpha and the nucleus paragigantocellularis lateralis (Fields et al. 1991), and it receives inputs from the hypothalamus, cortical regions and the limbic system (Ossipov and Porreca 2005). Neurons in RVM then project along the dorsolateral funiculus (DLF) to the dorsal horn. Exogenous opiates imitate endogenous opioids and induce analgesia by acting upon PAG and RVM in addition to the spinal dorsal horn (Ossipov and Porreca 2005). RVM contains so-called on- and off-cells. Off-cells are thought to exert descending inhibition of nociception, because whenever their activity is high there is an inhibition of nociceptive transmission, and because decreases in off-cell firing correlate with increased nociceptive transmission. On-cells instead seem to facilitate nociceptive mechanisms at the spinal dorsal horn. Thus, RVM seems to generate antinociception and facilitation of pain transmission (Gebhart 2004; Ossipov and Porreca 2005). Ultimately, spinal bulbospinal loops are significant in setting the gain of spinal processing (Porreca et al. 2002; Suzuki et al. 2002).

A particular form of descending inhibition of wide dynamic range (WDR) neurons is the “diffuse noxious inhibitory control” (DNIC). When a strong noxious stimulus is applied to a given body region, nociceptive neurons with input from that body region send impulses to structures located in the caudal medulla (caudal to RVM), and this triggers a centrifugal inhibition (DNIC) of nociceptive WDR neurons located throughout the neuraxis (Le Bars et al. 1979a, b).

#### 4.2

##### **Changes of Descending Inhibition and Facilitation During Inflammation**

In models of inflammation, descending inhibition predominates over facilitation in pain circuits with input from the inflamed tissue, and thus it attenuates primary hyperalgesia. This inhibition descends from RVM, LC and possibly other supraspinal structures, and spinal serotonergic (from RVM) and noradrenergic (from LC) mechanisms are involved. By contrast, descending facilitation predominates over inhibition in pain circuits with input from neighbouring tissues, thus facilitating secondary hyperalgesia. Reticular nuclei located dorsally to RVM also participate in facilitation of secondary hyperalgesia. Le-

sion of these nuclei completely prevents secondary hyperalgesia (Vanegas and Schaible 2004).

In the RVM, excitatory amino acids mediate descending modulation in response to transient noxious stimulation and early inflammation, and they are involved in the development of RVM hyperexcitability associated with persistent pain (Heinricher et al. 1999; Urban and Gebhart 1999). As in the spinal cord, increased gene and protein expression and increased phosphorylation of NMDA and AMPA receptors take place in RVM (Dubner 2005; Guan et al. 2002).

A hypothesis is that messages from the inflamed tissue are amplified and relayed until they reach the appropriate brain stem structures. These in turn send descending impulses to the spinal cord, dampen primary hyperalgesia and cause secondary hyperalgesia. It is also possible that the “secondary neuronal pool” becomes hyperexcitable as a result of intraspinal mechanisms and that descending influences mainly play a contributing, yet significant, role in secondary hyperalgesia. Thus, during inflammation descending influences are both inhibitory and facilitatory, but the mix may be different for primary and secondary hyperalgesia and may change with time (Vanegas and Schaible 2004).

### 4.3

#### **Changes of Descending Inhibition and Facilitation During Neuropathic Pain**

Peripheral nerve damage causes primary hyperalgesia and allodynia that seem to develop autonomously at the beginning but need facilitation from RVM for their maintenance. CCK<sub>B</sub> receptor activation, as well as excitation of neurons that express  $\mu$ -opioid receptors in RVM, is essential for maintaining hyperexcitability in the primary neuronal pool (Porreca et al. 2002; Ossipov and Porreca 2005; Vanegas and Schaible 2004). “Secondary neuronal pools” are subject to a descending inhibition that is induced by the nerve damage and stems from the PAG. In contrast with inflammation, facilitation prevails in the primary while inhibition prevails in the secondary pool (Vanegas and Schaible 2004).

## 5

### **Generation of the Conscious Pain Response in the Thalamocortical System**

The conscious pain response is produced by the thalamocortical system (Fig. 2). Electrophysiological data and brain imaging in humans have provided insights into which parts of the brain are activated upon noxious stimulation. As pointed out earlier, pain is an unpleasant sensory and emotional experience, and these different components of the pain response are produced by different networks. The analysis of the noxious stimulus for its location, duration and intensity is the sensory-discriminative aspect of pain. This is produced in the lateral thalamocortical system consisting of relay nuclei in the lateral thalamus and

the areas SI and SII in the post-central gyrus. In these regions innocuous and noxious stimuli are discriminated (Treede et al. 1999).

The second component of the pain sensation is the affective aspect, i.e. the noxious stimulus is unpleasant and causes aversive reactions. This component is produced in the medial thalamocortical system, which consists of relay nuclei in the central and medial thalamus, the anterior cingulate cortex (ACC), the insula and the prefrontal cortex (Treede et al. 1999; Vogt 2005). These brain structures are part of the limbic system, and the insula may be an interface of the somatosensory and the limbic system. Even when destruction of the somatosensory cortex impairs stimulus localization, pain affect is not altered. It should be noted that limbic regions are not only involved in pain processing. In particular the ACC is activated during different emotions including sadness and happiness, and parts of the ACC are also involved in the generation of autonomic responses (they have projections to regions that command autonomic output systems). Other cingulate regions are involved in response selection (they have projections to the spinal cord and the motor cortices) and the orientation of the body towards innocuous and noxious somatosensory stimuli. A role of the ACC in the process of memory formation/access has also been put forward (Vogt 2005).

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