Emerging Concepts of Pain Therapy Based on Neuronal Mechanisms

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Contents

Abstract

Current pain treatment is successful in many patients, but nevertheless numerous problems have to be solved because still about 20 % of the people in the population suffer from chronic pain. A major aim of pain research is, therefore, to clarify the neuronal mechanisms which are involved in the generation and maintenance of different pain states and to identify the mechanisms which can be targeted for pain treatment. This volume on pain control addresses neuronal pain mechanisms at the peripheral, spinal, and supraspinal level which are thought to significantly contribute to pain and which may be the basis for the development of new treatment principles. This introductory chapter addresses the types of pain which are currently defined based on the etiopathologic considerations, namely physiologic nociceptive pain, pathophysiologic nociceptive pain, and neuropathic pain. It briefly describes the structures and neurons of the nociceptive system, and it addresses molecular mechanisms of nociception which may become targets for pharmaceutical intervention. It will provide a frame for the chapters which address a number of important topics. Such topics

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are the concept of hyperalgesic priming, the role of voltage-gated sodium channels and nerve growth factor (NGF) in different inflammatory and neuropathic pain states, the hyperalgesic effects of NGF in different tissues, the contribution of proteinase-activated receptors (PARs) to the development of pain in several chronic pain conditions, the role of spinal NO and of glial cell activation in the generation and maintenance of inflammatory and neuropathic pain, the potential role of spinal inhibitory interneurons, the endogenous endocannabinoid system, and the importance of nonneuronal immune mechanisms in opioid signaling in the control of pain, the influence of spinal mechanisms on the expression of peripheral inflammation, the role of the amygdala and their connections to the medial prefrontal cortex in pain states, the experimental methods to test central sensitization of the nociceptive system in humans, and differences and similarities of the neuronal systems of pain and itch. Finally it will be discussed that both the concentration on single key molecules of nociception and the interference with disease-related mediators may provide novel approaches of pain treatment.

Keywords

Nociceptive pain • Neuropathic pain • Nociceptive system • Peripheral sensitization • Central sensitization • Nociceptor • Pain mechanisms

Pain therapy is an important need in most fields of medicine because numerous diseases are associated with significant pain. Although pain treatment is successful in many patients, numerous problems still have to be solved. An impressive fact is that about 20 % of the people in the population suffer from chronic pain. According to epidemiological studies, chronic pain is most frequent in the musculoskeletal system, and osteoarthritis pain and low back pain are the leading causes (Breivik et al. 2006).

There are numerous reasons for the existence of chronic pain and the failure of pain therapy. Concerning drug therapy, we have only a limited spectrum of drugs which are available for pain treatment. It is largely based on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis and on the use of opioids. In addition, for the treatment of neuropathic pain, drugs are used which reduce the neuronal excitability. The available drugs may not be sufficient to achieve long-lasting pain relief. Furthermore, they have side effects which limit their use in the long term. Intense pain research is, therefore, necessary to improve the situation.

Pain research has several aims. A major first aim is to clarify the neuronal mechanisms which are involved in the generation and maintenance of pain. Based on the numerous studies in different disciplines, it is quite clear that pain is the result of complex mechanisms which interact in many ways. Pain is determined by neurophysiological mechanisms in the nociceptive system as well as by other components such as psychological and social factors. The key to better pain therapy

is an advanced understanding of the processes which are integrated in order to produce the clinical symptom pain. The second major aim is to identify the mechanisms which can be targeted for pain treatment. However, due to the complexity of factors contributing to pain, pain treatment is not limited to the use of drugs. For the treatment of chronic pain, rather interdisciplinary approaches are suitable which include drug therapy, physiotherapy, psychotherapy, and others.

This volume on pain control addresses neuronal pain mechanisms at the peripheral, spinal, and supraspinal level which are thought to significantly contribute to pain and which may be the basis for the development of new treatment principles. Naturally it will not be possible to cover all relevant areas in this volume.

Related to the sensation of pain is the sensation of itch (see Schmelz 2015). Pain and itch are generally regarded antagonistic as painful stimuli such as scratching suppress itch. Several findings are in agreement with the specificity theory for itch, but there are also considerable overlaps of mechanisms of pain and itch, and therefore, research concepts should address the common mechanisms.

1 Pathophysiological Background

1.1 Types of Pain

From the etiopathological point of view, currently three types of pain are distinguished (Schaible and Richter 2004). If noxious stimuli threaten normal tissue, ***physiologic nociceptive pain*** is elicited. Usually intense mechanical (noxious pressure, noxious movements, etc.) or thermal stimuli (noxious heat, noxious cold) are necessary to activate the nociceptive system. This type of pain protects the body from being damaged.

In the course of inflammation or tissue injury, ***pathophysiologic nociceptive pain*** is evoked. It is characterized by mechanical and/or thermal allodynia and hyperalgesia. The threshold for elicitation of pain is lowered into the normally innocuous range, with the consequence that normally non-painful stimuli elicit pain. Pathophysiologic nociceptive pain is the most frequent cause for seeking medical treatment. The nociceptive system undergoes significant changes, but overall, its functions are intact. This pain is often dependent on stimulation, i.e., evoked by load. Pathophysiologic nociceptive pain has the purpose to prevent the tissue from further damage and to support healing processes. Under suitable conditions, it disappears after successful healing.

The third type of pain results from damage or disease of neurons of the nociceptive system. In this case nerve fibers themselves are afflicted, and therefore, this type of pain is called ***neuropathic pain***. This form of pain is abnormal, often aberrant, because it does not signal tissue inflammation or tissue injury, and it may be combined with loss of the normal nerve fiber function. Neuropathic pain is useless because it does not serve as a warning signal for body protection. Damage or diseases of the peripheral as well as of the central nociceptive system can elicit neuropathic pain.

1.2 The Nociceptive System

Pain is produced by the activation of the nociceptive system, the part of the nervous system which is specialized for the detection and processing of noxious stimuli. In the brain the nociceptive system cooperates with other systems allowing bidirectional interactions between the nociceptive and other systems. The peripheral nociceptive system provides the sensors for noxious stimuli; the central nervous system processes the nociceptive input and produces the conscious sensation of pain.

The ***peripheral nociceptive system*** is composed of the nociceptive nerve fibers which innervate the tissue. Peripheral nociceptors are either C-fibers or A∂-fibers, and their sensory endings in the tissue are free nerve endings. Most nociceptive sensory fibers are polymodal and respond to noxious mechanical and thermal stimuli as well as to a variety of chemical stimuli. The excitation threshold of these nerve fibers is near or at the noxious (tissue damaging) range, and the fibers encode noxious stimuli of different intensities by their discharge frequencies. In order to sense noxious stimuli, nociceptive sensory endings are equipped with ion channels which open upon the application of noxious stimuli. Some of these transduction molecules were identified, but there are still numerous gaps in knowledge (see Sect. 1.4). By opening such ion channels, noxious stimuli depolarize the sensory neurons. If the so-evoked depolarizing sensor potentials reach a sufficiently high amplitude, they trigger the opening of sodium channels and elicit action potentials which propagate along the nerve fiber and cause synaptic activation of nociceptive neurons in the spinal cord (or of the brain stem for nociceptive input from the head) (Schaible and Richter 2004).

The ***central nociceptive system*** consists of the nociceptive neurons in the spinal cord and in different supraspinal structures which are activated by noxious stimuli. ***Nociceptive neurons in the spinal cord*** form either ascending tracts which transmit the nociceptive information to the thalamus and the brain stem, or they are local interneurons which activate neurons within the same or adjacent segments. The spinothalamic tract ascends to the ventrobasal complex of the thalamus which is a relay nucleus on the way to the sensory cortex. Branches of the spinothalamic tract or other ascending tracts project to the brain stem, e.g., to the parabrachial nucleus which forms a pathway to the amygdala (Bushnell et al. 2013). They form also connections to brain stem nuclei which are the origin of the descending inhibitory and excitatory systems (Ossipov et al. 2010).

Nociceptive neurons in the thalamocortical system generate the conscious pain experience. Currently a distinction is made between the lateral system and the medial system. The lateral system consists of neurons in the ventrobasal nucleus of the thalamus and in the cortical areas S1 and S2, i.e., the somatosensory cortex. The activation of these neurons is thought to generate the sensory discriminative component of pain, i.e., the sensory analysis of the noxious stimulus. The medial system consists of neurons in the medial part of the thalamus and projections to the insula, the anterior cingulate cortex, and the forebrain. These pathways generate the affective emotional component of pain, the unpleasantness and the suffering, and

they are involved in the generation of behavioral responses to pain (Treede et al. 1999; Vogt 2005). Nociceptive stimuli also activate the amygdala which is a major site for the generation of fear (Duvarci and Pare 2014). The thalamocortical nociceptive system interacts with numerous other systems which are involved in brain functions, e.g., neuronal circuits which are involved in the generation of emotions and others (Bushnell et al. 2013). A well-known consequence of such interactions is the occurrence of depression during pain states.

The brain stem forms a ***descending system*** which generates ***descending inhibition*** and ***descending excitation***. The nucleus of origin of descending inhibition is the periaqueductal gray which projects to the rostroventral medulla. From there tracts descend to the spinal cord where they influence the spinal nociceptive processing. The descending inhibitory system serves as an endogenous pain control system which keeps the nociceptive system under control. It can be activated from the brain and is, e.g., active during placebo responses (Ossipov et al. 2010).

In the chapter on **itch**, Schmelz addresses the differences and similarities of the neuronal systems of pain and itch. Separate specific pathways for itch and pain processing have been uncovered, and several molecular markers at the primary afferent and spinal level have been established in mice that identify neurons involved in the processing of histaminergic and non-histaminergic itch. However, in addition to broadly overlapping mediators of itch and pain, there is also an evidence for overlapping functions in primary afferents. Nociceptive primary afferents can provoke itch when activated very locally in the epidermis, and sensitization of both nociceptors and pruriceptors has been found following local nerve growth factor (NGF) application in volunteers. Thus, the mechanisms that underlie the development of chronic itch and pain including spontaneous activity and sensitization of primary afferents as well as spinal cord sensitization may well overlap to a great extent (Schmelz 2015).

1.3 Neuronal Mechanisms of Pathophysiologic Nociceptive and Neuropathic Pain

In clinically relevant pain states, the nociceptive system undergoes significant changes at the peripheral as well as the central level. Pathophysiologic nociceptive pain and neuropathic pain involve different as well as common mechanisms. Figure 1 displays major changes which are observed in chronic pain states.

At the peripheral level distinct processes were observed which characterize pathophysiologic nociceptive and neuropathic pain. The hallmark of pathophysiologic nociceptive pain, e.g., pain during inflammation or after tissue injury, is **peripheral sensitization**. Nociceptive nerve fibers exhibit a lowering of their excitation threshold for the response to mechanical and/or thermal stimuli and increased firing frequencies during the application of stimuli of noxious intensities. Such processes were characterized in the skin, muscle, joint, and visceral organs (Schaible and Richter 2004). Molecular mechanisms of peripheral sensitization are addressed in Sect. 1.4 (see below). More recently, the concept of **hyperalgesic**

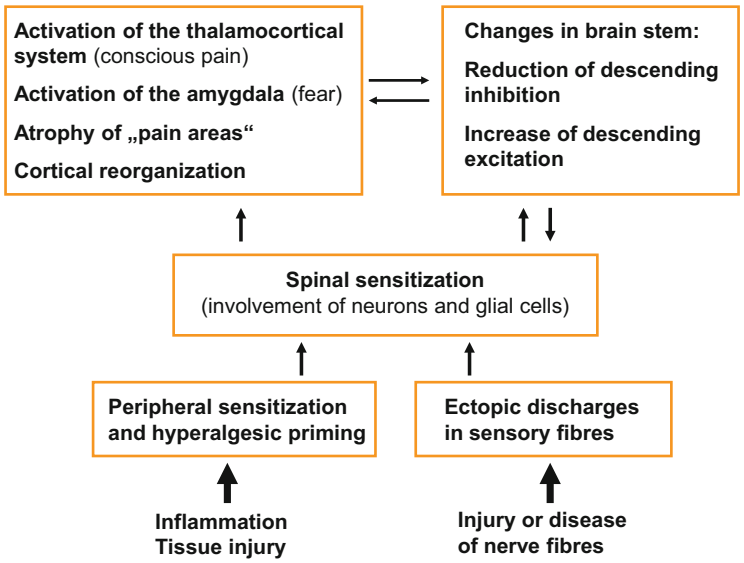

Fig. 1 Changes in the nociceptive system during pathophysiologic nociceptive pain and neuropathic pain. Spinal sensitization and increased hyperexcitability at the supraspinal level form the process of central sensitization

priming was introduced (see Kandasamy and Price 2015). Priming arises from an initial injury and results in the development of a remarkable susceptibility to normally subthreshold noxious inputs causing a prolonged pain state in primed animals. Priming increases the sensitization process which is evoked by sensitizing mediators. As an example, application of prostaglandin E2 to normal tissue causes a short-lasting sensitization of nociceptors if applied before injury or priming. However, if the neurons were primed, e.g., by interleukin-6, NGF, and other priming stimuli, prostaglandin E2 will cause a long-lasting sensitization (see Kandasamy and Price 2015).

A frequent process of neuropathic pain at the peripheral level is the generation of **ectopic discharges**. These action potentials can be elicited at the lesion site of the nerve fibers, but they can also be generated in the soma of the lesioned neurons (Devor 2009). Underlying mechanisms are changes in the expression of ion channels, actions of inflammatory mediators on lesioned fibers, and effects of the sympathetic nervous system on lesioned nerve fibers. In the latter case the neuropathic pain may be sympathetically maintained (Schaible and Richter 2004).

Peripheral nociceptive processes often trigger changes in the spinal cord which are called **central sensitization**. The changes in the spinal cord provide a gain of the nociceptive processing at the spinal site (Cervero 2009; Woolf and Salter 2000). Nociceptive spinal cord neurons which receive increased input from inflamed regions show the following phenomena: a lowering of threshold, increased responses to innocuous and noxious stimuli, and an expansion of the receptive

fields (Schaible et al. 2009). In the sensitized state, more spinal cord neurons show responses to a stimulus applied to a specific peripheral site. These changes reflect an increase of the synaptic processing including the suprathreshold activation of synapses which may be too weak in the normal state to depolarize the neuron sufficiently. In many aspects these processes are similar to the **long-term potentiation** which was characterized as a major process of memory formation in the hippocampus (Sandkühler 2000). Central sensitization is also thought to occur in neuropathic pain states.

Several cell types may contribute to the spinal sensitization. First, the sensitization of peripheral nociceptors increases the sensory input into the spinal cord, thus providing a stronger presynaptic component of synaptic activation. Second, postsynaptic spinal cord neurons are rendered hyperexcitable by the activation of NMDA and other receptors (Sandkühler 2000; Woolf and Salter 2000). Third, glial cells may be activated and produce cytokines and other mediators which facilitate the spinal processing. Glial cells are strongly activated in neuropathic pain states, but they may also contribute to inflammatory pain (McMahon and Malcangio 2009). The involvement of glial cells in pain states is addressed by Old et al. (2015). Fourth, the activity of inhibitory interneurons may be reduced. The inhibitory neurons in the spinal cord and the mechanisms by which the inhibitory control is decreased or lost are addressed by Todd (2015). The spinal sensitization and the resulting thalamocortical processing are thought to underlie the observation that in many pain states the pain becomes widespread (Phillips and Clauw 2013). The significance of central sensitization in humans under clinically relevant conditions, and the experimental methods to test central sensitization in humans, will be addressed by Arendt-Nielsen (2015).

Ascending nociceptive information activates the thalamocortical system. During chronic pain states significant changes of this system were observed in patients using fMRI. Remarkably, many chronic pain states such as chronic osteoarthritic pain are associated with a so-called **atrophy** of the regions in which pain is processed. The underlying cellular mechanisms have not been identified. Interestingly, this atrophy seems to be reversible because after successful treatment of pain, the brain structures show a normalization (Bushnell et al. 2013; Gwilym et al. 2010; Rodriguez-Raecke et al. 2009). Under neuropathic conditions the cortex may show a **reorganization** with significant changes in the cortical maps. Such changes were, e.g., observed during phantom limb pain.

As already mentioned, ascending tracts not only activate the thalamocortical system. They also activate the amygdala via the parabrachial nucleus. Further input to the amygdala is provided by the nerve fibers from the thalamus and from the cortex (Duvarci and Pare 2014). The amygdala is key nuclei in the generation of **fear**, and they can be activated in pain conditions (Kulkarni et al. 2007). In this volume, the role of the amygdala and their connections to the medial prefrontal cortex (mPFC) in pain states will be addressed by Neugebauer (2015). Pain-related mPFC deactivation results in cognitive deficits and the failure of inhibitory control of amygdala processing. Impaired cortical control allows the uncontrolled persistence of amygdala pain mechanisms.

Neural pathways descending from the brain stem mediate inhibition and facilitation of nociceptive spinal cord neurons (Ossipov et al. 2010; Vanegas and Schaible 2004). During severe chronic pain, a **reduction of descending inhibition**, in particular the diffuse inhibitory noxious control (DNIC), was reported (Kosek and Ordeberg 2000; Lewis et al. 2012). In addition, **descending facilitation** may contribute to pain, in particular during neuropathic pain (Vanegas and Schaible 2004). Thus, descending inhibitory systems from the brain stem may be less effective and/or descending excitatory systems from the brain stem may be overactive during chronic pain. These changes may be (partly) reversible after successful pain treatment (Kosek and Ordeberg 2000).

Effects of the nervous system on inflammation. It must be noted that the importance of the nociceptive nervous system extends beyond the generation of pain. The nervous system is able to influence inflammatory processes in the organs. Such influences are mediated by the efferent effects of nociceptive sensory afferents which produce neurogenic inflammation, by fibers of the sympathetic and parasympathetic nervous system, and by neuroendocrine influences (Schaible and Straub 2014). Spinal hyperexcitability is not only important for pain generation (see above). It plays also a role in the regulation of joint inflammation (Waldburger and Firestein 2010). In this volume this topic will be addressed by Sorkin (2015). Both pro- and anti-inflammatory feedback loops can involve just the peripheral nerves and the spinal cord or can also include more complex, supraspinal structures such as the vagal nuclei and the hypothalamic–pituitary axis.

1.4 Molecular Mechanisms of Pain

Molecular mechanisms of nociception are of considerable interest for pharmacologic approaches, and therefore, they are particularly addressed in this volume. The peripheral nociceptor as well as the spinal cord and the amygdala are in the focus.

Nociception in the periphery consists of two elementary processes, the transduction of stimuli (the generation of a sensor potential by the impact of a noxious stimulus) and the transformation of the sensor potential into a series of action potentials. Noxious stimuli are mechanical or thermal (heat and cold), and also some chemical mediators (e.g., bradykinin or H^+) cause pain. The chemosensitivity of nociceptors is particularly important for the process of sensitization (and priming).

For the transduction of thermal stimuli into sensor potentials, ion channels of the transient receptor potential (TRP) family are responsible. While the involvement of TRPV1, TRPV2, and TRPM8 in the sensation of noxious heat (TRPV1 and TRPV2) and innocuous cold (TRPM8) has been established, the significance of other TRP channels in thermo(noci)ception is not that clear. For two TRP channels (TRPA1 and TRPV4), a role in mechanical hyperalgesia is being discussed (Kwan et al. 2009; Levine and Alessandri-Haber 2007; Malsch et al. 2014; Segond von Banchet et al. 2013) although these channels may not be the transduction molecules involved in the "normal mechanonociception." The current knowledge on the

involvement of TRP ion channels in the sensation of noxious heat and noxious cold and of the involvement of these ion channels in the generation of thermal hyperalgesia has been summarized (Basbaum et al. 2009; Julius 2013; Stein et al. 2009) and is not the topic of this volume.

Some chemicals can also open ion channels. For example, H^+ triggers the opening of acid-sensing ion channels (ASICs), and capsaicin opens TRPV1. Most mediators, however, activate membrane receptors and are thereby involved in the sensitization of nociceptive neurons (see below).

The sensor potential triggers the generation of action potentials. For action potentials voltage-gated sodium channels are essential. In nociceptive neurons, mainly the sodium channels $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, and under neuropathic conditions $Na_v1.3$, are expressed (Waxman and Zamponi 2014). $Na_v1.7$ is activated by slow, subtle depolarization close to the resting potential, and it thus sets the gain on nociceptors. $Na_v1.8$, which shows depolarized voltage dependence, produces most of the current responsible for the action potential upstroke, and it supports repetitive firing. $Na_v1.9$ does not contribute to the action potential upstroke but depolarizes the cells and prolongs and enhances small depolarization thus enhancing excitability (Waxman and Zamponi 2014). In this volume Habib et al. (2015) will address the role of these ion channels in different inflammatory and neuropathic pain states. They show that particular Na_v ion channels are involved in different pathophysiologic states. Because Na^+ channel blockers are thought to be promising targets for new analgesics (Gold 2008), such knowledge is important for the understanding of which blocker might be suitable under the particular conditions.

When neurons are sensitized both the channels of transduction and the voltage-gated ion channels, in particular the Na^+ channels, show changes such that the excitability is enhanced (Linley et al. 2010; Schaible et al. 2011). Some mediators such as prostaglandin E2 change the opening properties of TRPV1 and of sodium channels such that weaker stimuli are sufficient to open the ion channels. The effect of prostaglandin E2 is mediated by G protein-coupled receptors which activate second messengers in the nociceptors (Hucho and Levine 2007), and these second messenger systems change the opening properties of the ion channels.

While prostaglandins are known for a long time as sensitizing molecules, more recent research revealed a number of other receptor types in nociceptive sensory neurons which are of great importance for the sensitization. It was shown that proinflammatory cytokines such as TNF-α, interleukin-6, and interleukin-17 induce a persistent state of sensitization in C-fibers (Brenn et al. 2007; Richter et al. 2010, 2012). Cytokines are thought to play a significant role in the generation of inflammatory and neuropathic role (Schaible et al. 2010; Sommer and Kress 2004; Üceyler et al. 2009). Interleukin-6 is thought to be an important molecule of hyperalgesic priming (see Kandasamy and Price 2015).

NGF and its receptor trkA were discovered as suitable targets for pain treatment. A single application of an antibody to NGF was shown to provide significant pain relief in osteoarthritis for several weeks (Lane et al. 2010). NGF has a variety of actions on nonneuronal cells and sensory neurons which regulate the excitability in

the long term (Bennett 2007). In this volume Mizumura and Murase (2015) address the hyperalgesic effects of NGF in different tissues and in inflammatory and neuropathic pain states, and they address the mechanisms involved.

Proteinase-activated receptors (PARs) are a family of G protein-coupled receptor that is activated by extracellular cleavage of the receptor in the N-terminal domain. This slicing of the receptor exposes a tethered ligand which binds to a specific docking point on the receptor surface to initiate intracellular signaling. McDougall and Muley summarize how serine proteinases activate PARs leading to the development of pain in several chronic pain conditions. The potential of PARs as a drug target for pain relief is discussed (McDougall and Muley 2015).

Excitatory synaptic transmission in the spinal cord under basal conditions is mediated by the transmitter glutamate, the transmitter of nociceptive sensory neurons. Central sensitization is also dependent on glutamate, in particular acting on NMDA receptors. However, numerous other transmitters and mediators are involved in the complex signaling in the spinal cord (e.g., NK1 receptors for substance and CGRP receptors) (Woolf and Salter 2000). Other mediators such as spinal prostaglandins contribute to spinal sensitization (Bär et al. 2004). The particular role of NO to nociceptive spinal cord signaling will be addressed by Schmidtko (2015). The role of mediators involved in glial cell activation and functions will be addressed by Old et al. (2015).

Under normal conditions, excitatory and inhibitory synaptic mechanisms are presumably in a balanced activity state. Such inhibition is provided by specific local inhibitory interneurons (see Todd 2015), but it may also be provided by mediators which act in a feedback manner from activated neurons. Such inhibitory control is, e.g., provided by endocannabinoids which are addressed in this volume by Woodhams et al. (2015). Cannabinoid 1 (CB_1) receptors are found at presynaptic sites throughout the peripheral and central nervous systems, while the CB_2 receptor is found principally (but not exclusively) on immune cells. The endocannabinoid (EC) system is now known to be one of the key endogenous systems regulating pain sensation, with modulatory actions at all stages of pain processing pathways. As already discussed, pain states may involve a reduction of inhibitory mechanisms.

A particular interesting aspect is that some mediators may exert excitatory as well as inhibitory actions, depending on the functional context. An example is the change of GABAergic inhibitory mechanisms in neuropathic pain states (see Todd 2015). However, even mediators such as prostaglandin E2 which are usually considered excitatory may provide antinociception when pain pathways are activated, by the activation of receptor subtypes which are coupled to inhibitory signaling pathways (Natura et al. 2013). In this volume Schmidtko (2015) reports about both the pro- and antinociceptive effects of NO signaling resulting from a different downstream signaling.

Spinal cord mechanisms may even alter the antinociceptive effect of potent analgesic drugs. Opioids are considered the gold standard for the treatment of moderate to severe pain. However, heterogeneity in analgesic efficacy, poor potency, and side effects are associated with opioid use. Traditionally opioids are thought to exhibit their analgesic actions via the activation of the neuronal G

protein-coupled opioid receptors. However, neuronal activity of opioids cannot fully explain the initiation and maintenance of opioid tolerance, hyperalgesia, and allodynia. In this volume Thomas et al. (2015) report the importance of nonneuronal mechanisms in opioid signaling, paying particular attention to the relationship of opioids and immune signaling.

Abnormally enhanced output from the CeLC of the **amygdala** is also the consequence of an imbalance between excitatory and inhibitory mechanisms (see Neugebauer 2015). Impaired inhibitory control mediated by a cluster of GABAergic interneurons in the intercalated cell masses (ITC) allows the development of glutamate- and neuropeptide-driven synaptic plasticity of excitatory inputs from the brain stem (parabrachial area) and from the lateral–basolateral amygdala network (LA-BLA, site of integration of polymodal sensory information).

2 Conclusion

It is increasingly evident how many different neuronal and molecular mechanisms contribute to the expression of pain, in particular in clinically relevant pain states. We begin to understand some mechanisms of pain vulnerability (Denk et al. 2014). The complexity of pain processing and related neuronal events puts a considerable challenge to the development of new therapeutic strategies. Is the focus on single key molecules such as a particular sodium channel an appropriate therapeutical approach or should one aim to interfere with disease-related mediators such as NGF or cytokines? The answer to this crucial question is not straightforward. Both types of drugs have been proven useful in medical therapy. Local anesthetics targeting specifically sodium channels can interrupt pain (usually for a short time only), but on the other hand, the use of antibodies to particular cytokines which have numerous actions is extremely potent in the therapy of rheumatic diseases such as rheumatoid arthritis. Thus, future pain therapy should provide effective treatments using either specific drugs with the aim of interfering with specific nociceptive processes or using drugs which have the potency of long-term modification of pain mechanisms.

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