The Physiology of Pain Mechanisms: 
From the Periphery to the Brain

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Pain is a dynamic phenomenon. From the periphery to the brain, the nociceptive signal will be modulated at all levels of the central nervous system (CNS). This plasticity speaks to the ability to adapt and change within the nervous system. The current science regarding concepts of pain mechanisms also takes into account genetic and environmental factors that will influence the development of persistent pain. Moreover, the maintenance of chronic pain is not only the result of continued and increased nociceptive activity mostly arising at the peripheral site of pathology, but also depends on additional changes within the CNS, such as an increase of excitatory or reduction of inhibitory endogenous pain modulation mechanisms.

Multiple endogenous excitatory and inhibitory mechanisms have been identified [1]. This article introduces the scientific basis for the understanding of pain mechanisms and highlights the importance of endogenous excitatory and inhibitory controls within the CNS. These innate control systems have an impact on the evolution of chronic pain and may be manipulated to alter the pain process, and therefore have implications regarding treatment. Rheumatic pain, particularly as seen in longstanding osteoarthritis, may be considered the prototype of chronic pain. Additionally, inflammatory arthritic diseases also account for important pain complaints and suffering across all ages. Understanding neurophysiologic mechanisms involved in the development and maintenance of pain will help the clinician to devise a more effective treatment plan guided by pathophysiologic dysfunction.

From nociception to pain

A good way to understand the physiology of pain is to follow the nociceptive signal pathways from the periphery to the brain, with emphasis on
the integration and modulation of the nociceptive signal at different steps in the CNS (Fig. 1).

Mechanical, chemical, or thermal nociceptive stimulation will recruit peripheral nociceptors that conduct the nociceptive signal in the primary somatosensory neuron to the dorsal horn of the spinal cord. In the dorsal horn, the primary neuron will make a synaptic contact with the secondary or projection neuron. Secondary neurons form the spinothalamic (lateral) and spinoreticular (medial) tracts will immediately cross in the spinal cord and send afferent projections to higher centers. A large proportion of afferents will make a second synapse in the lateral and medial nuclei of the thalamus, which subsequently make synaptic contact with tertiary neurons. It is important to emphasize that the secondary neurons may also synapse with neurons in different nuclei of the brainstem, including the periaqueductal gray (PAG) and nucleus raphe magnus (NRM), areas involved in descending endogenous pain modulation. Tertiary neurons

![Diagram of nociceptive pathways](image)

Fig. 1. The nociceptive pathways from the periphery will conduct to the brain after two synaptic relays. The Aδ and C-fibers will make their first synapse with the projection neurons in the dorsal horn of the spinal cord. The secondary neurons will decussate immediately in the cord and conduct to the thalamic nuclei, where they will make the second synaptic contact. The third neurons will finally project to the somatosensory cortices for the sensory-discriminative component of pain, and to limbic structures (anterior cingulated cortex and insula) for the motivational component of pain. ACC, anterior cingulate cortex; NRM, nucleus raphe magnus; SI, SII, somatosensory cortices; PAG, periaqueductal gray.
from the thalamus send afferents to the primary and secondary somatosensory cortices (SI, SII). The SI and SII are involved in the sensory quality of pain, which includes location, duration, and intensity. Tertiary neurons also project to limbic structures, including the anterior cingulate cortex (ACC) and the insula, which are involved in the affective or emotional component of pain.

The various synaptic contacts with excitatory and inhibitory neurons at all levels of the CNS are important integration regions that are the target of most pharmacologic approaches.

The periphery: the nociceptors

An injury that causes a potential risk for the organism will activate free nerve endings that respond to nociceptive stimulation (Fig. 2). Most of these fibers are polymodal and will respond to different modalities, including mechanical, thermal, and chemical stimulation [2].

A nociceptive stimulation will initiate a cascade of events. Pronociceptive inflammatory molecules will be released into the periphery and will produce

<table>
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<tr>
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<th>Aβ</th>
<th>Aδ</th>
<th>C</th>
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<tr>
<td>Diameter</td>
<td>6 to 12 μ</td>
<td>1 to 5 μ</td>
<td>0.2 to 1.5 μ</td>
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<td></td>
<td>myelinated</td>
<td>myelinated</td>
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<tr>
<td>Conduction</td>
<td>35 to 75 M/s</td>
<td>35 to 75 M/s</td>
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<td>Role</td>
<td>Light touch, proprioception</td>
<td>Temperature, Nociception (mechanical, thermal)</td>
<td>Nociception (mechanical, thermal and chemical)</td>
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Fig. 2. The nociceptive afferent fibers can be separated according to their physical characteristics and conduction velocity. On this nerve section, where the myelin has been stained in black, one can see the large myelinated Aβ fibers, the smaller and myelinated Aδ fibers, and the unmyelinated C fibers. As seen in the table, the conduction velocity will increase with the diameter and thickness of the myelin sheet.
peripheral hyperalgesia. These pronociceptive inflammatory molecules originate in various blood cells (mastocytes, polymorphonuclear cells, and platelets) and include bradykinins, prostaglandins, histamine, serotonin, adenosine triphosphate, and also from immune cells which produce interleukins, interferon, and tumor necrosis factors [3–6]. Substance P and calcitonin gene related protein (CGRP), which act as neurotransmitters in the CNS, are also released into the periphery and act as proinflammatory factors in the periphery, favoring neurogenic inflammation [3].

Primary hyperalgesia: peripheral nociceptors hyperactivity

Injured tissues will release various substances, such as potassium, prostaglandins, histamine, or bradykinins that are pronociceptive, and will also invoke an immune response. These inflammatory and immune factors will sensitize the nociceptive receptors directly within the lesion and in the surrounding neurons [6]. Primary hyperalgesia, which follows the release of these factors, may be measured as a lowered pain threshold in and around the lesion. This has been demonstrated to occur in the area of arthritic joints both in animal studies and in human beings.

Sensory afference from periphery to spinal cord

Afferent fibers originating in the periphery fall into three groups: Ab fibers, C fibers, and Aδ fibers. The Ab fibers are large myelinated fibers that conduct at high speed and usually transmit non-nociceptive signals. They do, however, also participate in pain modulation, as will be explained later in this article. Nociceptor messages are mainly transmitted by the other two classes of fibers, the larger myelinated Aδ fibers and the thin unmyelinated C fibers. The nociceptors are frequently refer to by the characteristics of their fibers.

Myelination and increasing size of a nerve fiber facilitate the speed of conduction of the stimulus. The Aδ fibers conduct the signal relatively rapidly from the periphery to the spinal cord. Because of this rapid conduction velocity, they are responsible for the sharp localization of pain and for the rapid spinal response, which can be measured in the laboratory as the nociceptive reflex. In contrast, the C fibers, which have a slow conducting velocity, will mediate a second or dull aching pain.

Ab fibers

The Ab (or Aβ) fibers are principally involved in the conduction of non-nociceptive input, such as vibration, movement, or light touch. The Ab fibers are large myelinated fibers with a rapid conduction velocity (35 m–75 m per second). Besides conducting the non-nociceptive signal, the stimulation of Ab fibers will recruit inhibitory interneurones in the substantia gelatinosa of the dorsal horn of the spinal cord, which will inhibit nociceptive input at the same spinal segment. This mechanism is one of the fundamental components of the gate control theory, whereby an innocuous stimulus will reduce
the nociceptive input from the same region [7]. Besides playing a dynamic inhibitory role when recruited, the Ab fibers seem also to play a tonic inhibitory role on the nociceptive input. Blocking the input from these large fibers will result in an increased response to nociceptive stimuli [8].

\textit{A\delta fibers}

The \textit{A\delta} fibers are relatively large myelinated fibers with slower conduction velocity than the Ab fibers, but faster (5 m–30 m per second) than the C fibers. They represent the majority of the myelinated fibers. Two types of \textit{A\delta} fibers exist depending on the specificity of their responses to different stimulation [9]: the mechanonociceptors respond preferentially to intense and potentially harmful mechanical stimulation; the polymodal \textit{A\delta} fibers respond to mechanical, thermal, and chemical stimulation. However, the mechanonociceptor \textit{A\delta} fibers will also increase their discharge after intense thermal stimulation, a phenomenon known as hyperalgesia. Because of the rapid conduction velocity, the \textit{A\delta} fibers are responsible for the first pain sensation, a rapid pinprick, sharp, and transient sensation.

\textit{C fibers}

Because of their small caliber and lack of myelin, the conduction of the C fibers is relatively slow (0.5m–2 m per second). They represent three quarters of the sensory afferent input and are mostly recruited by nociceptive stimulation. However, they are also involved in non-nociceptive somatosensory information, such as in the sensation of pruritus [10], and paradoxically, in the perception of pleasant touch, as documented in a patient with a rare disease linked to a deafferentation of the myelinated sensory fibers [11].

\textit{First and second pain}

The conduction velocity differences between the \textit{A\delta} and C fibers can be appreciated when isolating the sensation of first and second pain (Fig. 3). Following a brief nociceptive stimulation, the \textit{A\delta} fibers will rapidly transmit a brief and acute pinprick-like sensation, perceived to be precisely located at the point of stimulation. It is this precision and fast conduction that will result in the nociceptive withdrawal reflex. Following this activity, C fibers will transmit their information with a relatively long delay (100 milliseconds to a second, depending on the stimulus location). This second sensory input results in a more diffuse deep pain sensation.

It is possible to isolate first and second pain in the laboratory. Using a blood pressure cuff, one can temporarily block trophic factors present in the blood from localizing to the nerves. The first fibers that will show reduced activity are those with largest diameter, including the \textit{A\delta} fibers. This allows the activity of C fibers to be isolated and independently studied. Following this procedure, a nociceptive stimulation, independent of the nature of the stimulation, hot, cold or mechanical, will be perceived with a certain delay as a deeper pain sensation.
The application of capsaicin, the hot pepper extract, will produce a burning sensation because of the activation of the vallinoid receptors on the C fibers. However, at higher doses, the C fibers will be blocked as a result of a specific action on ionic calcium channels, with resulting isolation of the Aδ fibers at the skin surface. This time, the same nociceptive sensation will be perceived as a sharp pinprick-like sensation without the second burning pain sensation.

Secondary neurons in the spinal cord

When recruited, the Aδ and C fibers transport their signal to the spinal cord, where they will have a first synaptic contact with secondary neurons that are principally located in the superficial zones of the dorsal horn (I, II) and lamina V [12]. Both nociceptive and non-nociceptive afferents to the spinal cord will also have synaptic contact with an important network of
inhibitory and excitatory interneurones that modulate the nociceptive signal before the secondary neuron projects to superior centers. The secondary neurons can be divided into two classes: the nociceptive specific neurons and the wide dynamic range (WDR) neurons [2,3,13].

Nociceptive specifics neurons

As indicated by their name, the nociceptive specific neurons respond only to nociceptive stimulation. They can be divided in two subclasses depending on their recruitment by A\(\delta\) or the combination of A\(\delta\) (or Ad) and C fibers.

Wide dynamic range neurons

WDR neurons respond gradually to stimuli ranging from innocuous to nociceptive. Their capacity to respond to both innocuous and nociceptive stimuli is related to the fact that they have received input from A\(\delta\) fibers, C fibers, and also Ab fibers (Fig. 4). Interestingly, the receptive field of WDR neurons is dynamic, as the name implies, and changes in conditions of persistent pain. Animal studies have shown that inflammatory pain will have multiple effects on the function of WDR neurons. Changes in the receptive field, the membrane permeability to ion exchange, and the discharge frequency of these neurons all suggest that they play a substantial role in the chronicity of pain [14].

Excitatory mechanisms: secondary hyperalgesia

Secondary hyperalgesia is a phenomenon that refers to sensitization that occurs within the CNS [13]. Repeated recruitment of C-fibers following an injury will produce central sensitization by changing the response properties of the membranes of secondary neurons. This will result in an increase of the firing rate, a phenomenon known as windup [15]. The high frequency recruitment of C fibers, either by increased repetitive stimuli or by a tonic stimulation [16], will then induce an increase of the perceived pain, even if the intensity of the stimulation remains constant. This spinal sensitization can persist for minutes, but can also be present for hours and even days [17]. The prolonged activation of the NMDA receptors will induce the transcription of rapidly expressed genes (c-fos, c-jun), resulting in sensitization of nociceptors. This neuronal plasticity of the secondary neuron will result in reduced recruitment threshold of secondary neurons in the spinal cord and produce hyperalgesic and allodynic responses that may persist even after the healing of the injury. Taking note of the impact of sensitization, an aggressive and early treatment plan to reduce pain will help in preventing ongoing chronic pain (see Fig. 4).

Excitatory mechanisms: temporal summation

The temporal summation paradigm is a good illustration of the importance of signal conduction in A\(\delta\) and C fibers [18]. In this paradigm, pain perception is compared with repeated stimulations at the same intensity
A

Ad and C fibers

Glutamate

NMDA

AMPA

Mg²⁺

K⁺, Na⁺

NK-1

Ab fiber

Spinothalamic projection secondary neuron

B

Ad and C fibers

Glutamate

NMDA

AMPA

Ca²⁺

Mg²⁺

K⁺, Na⁺

NO

Alodynia

Hyperalgesia

Sensitization

C-Fos

Ab fiber

Spinothalamic projection secondary neuron
but at different rates. The rationale is that high frequency of stimulation will produce a temporal summation of the C-fiber activity, as a result of the relatively slow conduction of these fibers. This temporal summation results in an increase in the perceived intensity of the second pain, which is related to C-fiber activity, without changing the perception of the first pain, related to Aδ fibers [19]. The accumulation of nociceptive activity will produce a transient change in the excitability of the spinal cord second neuron, or windup, that may lead to central sensitization [20]. However, windup, a transient effect related to the frequency of discharge from the primary neuron, is different from central sensitization [17].

Central sensitization refers to a phenomenon whereby the second neuron membrane permeability changes and responds at higher frequency when recruited by nociceptive (hyperalgesia) and non-nociceptive primary input (alldynia). Central sensitization is defined as an increase of excitability and spontaneous discharge at the dorsal horn neurons with an associated increase in the receptive field for these neurons. This phenomenon will principally affect the WDR neurons from the dorsal horn (see next section on the spinal cord neurons) and is dependent on the activity of the NMDA receptors [21,22]. Central sensitization may persist for prolonged periods after termination of stimulation and has important effect on the persistence of pain.

Excitatory mechanisms: spatial summation

Another important phenomenon in the CNS is spatial summation. The stimulation of a large territory will recruit more nociceptors than when a smaller area is stimulated and will result in more intense pain perception. It is worth noting that increasing the surface area that is stimulated recruits both excitatory and inhibitory mechanisms [23].

Clinical implications of temporal and spatial summation. It is possible to study the relative role of endogenous pain excitatory and inhibitory mechanism dysfunction in certain chronic pain conditions using temporal [24] and spatial summation [25]. The author and colleagues have examined this spatial summation paradigm in patients with fibromyalgia (FM), and have
observed no differences in pain perception between the increasing or decreasing nociceptive area, suggesting a deficit of endogenous pain modulation. This deficit was not present in patients with low back pain, suggesting that the deficit of endogenous pain modulation is not present in all chronic pain conditions [25]. A chronic pain condition may therefore be related to either hyperactivity of nociceptive activity or, conversely, to hypoactivity of endogenous pain inhibitory mechanisms at different levels of the CNS. Exploring the role of excitatory and inhibitory mechanism dysfunction in different patient populations will help to better characterize the underlying deficit and facilitate treatment choices.

Pain pathways from the spine to the superior centers

The secondary neuron travels to superior centers by two main pathways: the spinothalamic tract, which sends afferents to the lateral nuclei of the thalamus, and the spinoreticular tract, which send afferents to the medial thalamus and nuclei of the brainstem, including the NRM and the PAG, two nuclei involved in descending pain modulation [26]. A third pathway, from the medial dorsal cord (lemniscal) is mostly associated with non-nociceptive afference, but also conducts nociceptive afference from the viscera [27,28].

Sensory spinothalamic tract

The spinothalamic tract comprises the lateral part of sensory input and projects directly to the lateral nuclei of the ventrobasal thalamus (ventroposterolateral or VPL; ventroposteromedian or VPM). The projection neurons from the spinothalamic tract are primarily from lamina I and IV to VI of the spinal cord [29], and project to the contra lateral nuclei of the thalamus.

The fibers of the spinothalamic tract conduct rapidly and the projection neurons have relatively small receptive fields, directed toward regions of the thalamus and somatosensory cortex that have defined somatotopic representation. The spinothalamic tract has all the characteristics for localization of a sensory pathway [26].

Affective spinoreticular tract

Most afference from the spinoreticular tract is from the deep lamina VII and VIII of the spinal cord and projects to the medial nuclei of the thalamus, as well as to structures of the brainstem involved in pain modulation, including the PAG and NRM [26]. Unlike the spinothalamic tract, the spinoreticular tract projects to neurons having large receptive fields that may cover wide areas of the body and play a role in the memory and affective component of pain [26].

Thalamic organization

The secondary neurons from the spinal cord project to the thalamus. The thalamic nociceptive neurons are localized in two groups of nuclei: the
ventrobasal (VPL and VPM) and the centromedian nuclei. The ventrobasal nuclei project their tertiary neurons to the primary and secondary somatosensory cortices (SI, SII). The centromedian neurons project to structures of the limbic system. This simplified description of the thalamus projections suggests that the sensorial and motivational components of pain are organized early in the CNS.

Moreover, the thalamus also plays a role in certain chronic pain conditions. Upon stimulation of specific nuclei of the thalamus, patients have experienced memory recall of the sensory and affective component of a previous pain that had long since disappeared. This suggests that some thalamic neurons may conserve a past painful experience that can be masked by a circuitry of inhibitory interneurones [30]. It is therefore plausible that a localized stroke in the thalamus may destroy tonic inhibitory circuitry and unmask nociceptive activity, leading to the well-recognized painful clinical thalamic pain syndrome.

**Brain and pain**

Pain can only be experienced when nociceptive afference reaches the cortex. It is for this reason that the term nociception is used to describe the signal following a lesion, whereas pain is a complex perception requiring CNS activity.

A complex network of cortical structures is activated during pain perception. Similar to the thalamic nuclei, the cortex can be represented in a simplified way by subdivision into structures involved in either the sensory or the affective components of pain. Brain imaging has demonstrated four cortical structures important for the perception of pain [31,32]. There are the somatosensory cortex (SI) in the postcentral circumvolution of the parietal lobe, the secondary somatosensory cortex (SII) in the parietal operculum, the ACC above the corpus callosum circumvolution, and the insular cortex (IC) under the temporal and frontal lobes at the level of the Sylvian fissure. The first two structures (SI and SII) are mainly involved in the sensory discriminative aspect of pain, while the ACC and IC are associated with the affective component of pain.

Most brain imaging studies report an activation of the sensory and affective brain structures following a nociceptive stimulus, demonstrating that pain perception is a complex experience with emotion, cognitive factors, and previous experience playing an important role in perceived pain. It can therefore be understood why the clinician should address pain from both the physical as well as the emotional aspect.

**Endogenous pain modulation mechanisms**

As pain is a dynamic phenomenon, the nociceptive signal will be modulated at multiple levels of the CNS before pain is fully perceived. Because of the dynamic and plastic characteristics of the nervous system, pain
perception, especially in a chronic pain condition, will change over time, dependent on different factors. Pain perception is the final outcome of complex mechanisms that modulate the nociceptive afferent signal. The modulation of the nociceptive signal starts at the periphery and involves several CNS structures, including excitatory and inhibitory mechanisms from the brainstem, the autonomic nervous system, and the cortical structures responsible for the emotional and cognitive aspect of pain perception.

Based on knowledge of the neurophysiology of pain, one can conclude that the development and maintenance of chronic pain is dependent upon several factors. Persistent pain can arise from the activity of nociceptive afference, but can also be related to a reduction of endogenous inhibition or augmentation of endogenous excitatory mechanisms. The literature on central sensitization supports the importance of endogenous pain excitatory circuitry on the development and maintenance of pain. The excitatory and inhibitory roles played by different structures of the brainstem have been well documented [33–35].

**Endogenous excitatory mechanisms**

Primary afferents are normally activated by nociceptive stimuli that can potentially induce an injury and by pronociceptive activation triggered by the inflammatory response.

**Spinal excitatory mechanisms**

As previously described, excitatory mechanisms can induce a central sensitization at the spinal level. Spinal sensitization is defined as an increase in the excitability and spontaneous discharge of the nociceptive spinal neurons, augmentation of the receptive field, and an accentuated response of spinal neurons to nociceptive (hyperalgesia) and non-nociceptive (alldynia) input. Spinal sensitization depends on the activation of the NMDA receptors of the spinal neurons, which are activated by a sustained released of glutamate [21,22,36]. These neurophysiologic and neurochemical mechanisms involved in spinal sensitization are responsible for modification of the spinal nociceptive circuitry and contribute to the maintenance of pain.

**Descending excitatory mechanisms**

It is now well documented that several supraspinal excitatory and inhibitory mechanisms play a major role in pain perception and, most probably, in certain chronic pain conditions [1]. The work of Fields and colleagues [37] describing activation of “ON” cells and inhibition of “OFF” cells in the brainstem during nociceptive activity has demonstrated the importance of excitatory mechanisms in amplifying the nociceptive response.

Recent studies have also demonstrated that certain physiologic conditions, such as nociceptive hyperactivity, may change the usual neuronal response to specific neurotransmitters. A particular example is the
hyperalgesic effect that can be observed in some patients using opioid med-
ications, mostly at higher doses [38]. Therefore, drugs with opioid activity
could, under some circumstances, produce a completely opposite effect
and enhance pain by producing an hyperalgesic response [38,39]. The
same is also true for GABA, which has been clearly identified as an inhibi-
tory neurotransmitter, but in certain conditions may cause hyperpolariza-
tion of neurons [40]. These observations support the concept of pain as a
dynamic phenomenon. An understanding of these complex mechanisms
can help explain the clinical variability of response to treatments in patients
with chronic pain.

Endogenous inhibitory mechanisms

To better understand the role of endogenous pain inhibitory mechanisms
in the development and treatment of pain, one should appreciate three levels
of modulation in the CNS (Fig. 5): (1) spinal mechanisms producing local-
ized analgesia; (2) descending inhibitory mechanisms from the brainstem
producing diffuse inhibition and; (3) superior center effects that will either
modulate descending mechanisms or change the perception of pain by rein-
terpreting the nociceptive signal.

Spinal mechanisms

Since the proposal of the gate control theory by Melzack and Wall [7], the
modulation of nociceptive afference at entry into the spinal cord has been
well documented. This input may be increased or decreased at the level of
the spinal cord. The gate control theory hypothesizes that, among other
mechanisms, selective activation of non-nociceptive afferent Ab fibers will
recruit inhibitory interneurones in the substantia gelatinosa of the posterior
spinal cord, producing a localized analgesia and decreasing pain perception.
In contrast, in certain neuropathic pain conditions, the nociceptive second-
ary projection neurons will be recruited at high frequency to transmit a pain
signal following an innocuous stimulation, a phenomenon known as allody-
nia and increased pain perception. Certain pain conditions may also result
from a reduced efficacy of tonic inhibitory controls within the spinal cord
[41,42].

Diffuse noxious inhibitory controls

A few years after the gate control theory was proposed in 1965, Reynolds
[43] demonstrated that stimulation of the PAG produced a strong inhabi-
tion. The role of the rostroventral medulla in the modulation of pain has
since been well documented [33,44]. Regions, such as the PAG and the
NRM, have been identified as important serotonergic and noradrenergic
descending inhibitory pathways. These inhibitory pathways then recruit en-
kephalinergic interneurones in the spinal cord to produce the analgesic
response.
It was not until the end of the 1970s before a model, known as DNIC, was proposed. This model is based on the observation that a localized nociceptive stimulation can produce a diffuse analgesic effect over the rest of the body, an analgesic approach known as counter-irritation. In the DNIC model, Le Bars and colleagues [35,45] proposed that a nociceptive stimulus will send input to superior centers, but will also send afference to the PAG and NRM of the brainstem, recruiting inhibitory output at multiple levels of the spinal cord.
Animal studies demonstrate that a lesion of the dorsolateral funiculus, the main descending inhibitory pathway, will produce hyperalgesia, suggesting a role for tonic descending inhibition under normal conditions [46–48]. Certain clinical conditions are related to reduced endogenous inhibition. For example, the low concentration of serotonin and noradrenaline in the cerebrospinal fluid of patients with FM [49] suggests a deficit of DNIC, with increasing evidence corroborated by other studies [25,50–52].

Documenting the role of descending inhibitory mechanisms will help to better understand certain chronic pain conditions, such as FM. It will also help toward understanding the mechanism of action of pharmacologic approaches, such as the use of antidepressants in chronic pain conditions. Therefore, two key neurotransmitters involved in the DNIC response are those subserving the serotoninergic and noradrenergic mechanisms.

**Superior control centers**

There has been an increased appreciation of the role of supra-spinal centers in pain and pain modulation. Several cortical regions receive input from the spinothalamic tract and interact to produce the multidimensional experience of pain perception [53]. The use of brain imaging techniques has shown robust activation of certain cortical regions, including the primary and secondary somatosensory cortices, related to the sensory aspect of pain, and the ACC and IC for the affective component of the pain experience [54].

There is no doubt that cognitive manipulations, such as distraction, hypnosis, and expectation influence pain perception [54]. Hypnosis has been demonstrated to change both the sensory and affective component of pain perception. Subjects given the same nociceptive stimulus perceived both intensity as well as unpleasantness of pain differently, depending upon the suggestion given [55]. Using positron emission tomography to obtain brain activity images, activity of the primary somatosensory cortex was proportional to the perceived intensity of pain [56], whereas cingulate cortex activity reflected unpleasantness of pain [57]. These data confirm that a simple suggestion can change the brain activity related to pain perception. These concepts will be further described in the article by Keefe and colleagues on psychologic mechanisms, found elsewhere in this issue.

In a recent study, the author and colleagues were able to demonstrate that manipulating the expectation related to an analgesic procedure can totally reverse the analgesic effect of endogenous pain modulation and the related pain experience. By suggesting that a procedure that is normally analgesic would produce more pain, subjects indeed reported more pain. Therefore, suggestion was able to totally block the administered analgesic effect. Suggestion was also able to reverse the inhibition of the spinal nociceptive reflex (RIII) and of the brain activity measured by somatosensory
evoked potential [58]. These results support the idea that cognitive information can modulate the efficacy of endogenous pain modulation and emphasize the importance of the patient’s expectations regarding analgesia. This will be further addressed in the article by Pollo and Benedetti on placebo mechanisms found elsewhere in this issue.

Risk factors for developing chronic pain

Understanding factors other than the primary disease process that are involved in the development and maintenance of pain will help toward prevention of a chronic pain state. Three factors have been proposed to play a role in the chronicity of pain: personal predisposition, environmental factors, and psychologic factors. Paying attention to these elements will facilitate the management of patients with chronic pain.

Individual predisposition to chronic pain

Individual predisposition refers to the characteristics of a person that will influence their predisposition to pain and which are either acquired or innate. Under this category, are the role of gender and biological sex, the role of age, and the role of endogenous pain modulation responses.

Gender and sex

Women are more frequently affected by chronic pain syndromes than are men. The reason for this predisposition is probably multifactorial, with sex hormones likely playing an important role. Animal research supports differential responses between the sexes and supports the effect of sex hormones on pain experience. For instance, females show greater nociceptive responses than do males for the same stimulus, but this difference disappears after gonadectomy [59]. Moreover, if gonadectomized rats receive replacement hormones of the opposite sex, females receiving testosterone and males receiving estrogen and progesterone, they demonstrate the same nociceptive behavior attributable to the sex hormone status [60]. Interestingly, this influence of sex hormones seems also to be true in human beings, as differences in response to pain between men and women appears only after puberty and disappears after menopause or andropause [61,62].

Age

Even if we know that an increase in the prevalence of chronic pain among older individuals is partly because of progressive musculoskeletal degeneration that accompanies aging, decline in the efficacy of endogenous pain control systems may contribute to the high prevalence of pain in the elderly. Studies have shown a deficit of endogenous mechanisms with aging [63,64] and also a significant decrease of DNIC, which can occur as early as 50 years of age [65]. This reduction in endogenous pain control with
age probably contributes to the higher prevalence of chronic pain in the older population.

**Endogenous pain modulation**

The efficiency of the endogenous inhibitory system, which can be measured by DNIC, has been shown to be a good predictor for the development of chronic pain. More effective inhibitory control was correlated with less clinical pain [66]. The deficit of DNIC in FM but not in low back pain [25] also supports the role of DNIC in chronic pain, but may also be specific to certain pathologies.

**Genetic predisposition**

There is increasing evidence that some individuals are more prone to the development of chronic pain than others. Genetic predisposition to the development of pain and to the response to pain treatments is now well documented in the literature [67,68]. This genetic predisposition helps toward understanding the differential response between individuals to the development of chronic pain following an injury. The persistence of pain following an injury, which at times may be without objective pathology, such as occurs in whiplash injury, may be influenced by genetic factors. The same applies for certain treatments. It is well recognized by clinicians that different patients respond differently to individual analgesic medications with regard to both efficacy as well as side-effect profile.

**Environmental factors**

External stressors, history of previous pain [69], or abuse [70] are also good predictors of the development of chronic pain. For instance, it has been demonstrated that children born prematurely, receiving painful clinical interventions, will be more sensitive to pain later in life [71–73]. The mechanism by which these children may be sensitized to pain can be partly explained by deficits in pain inhibitory mechanisms. The author and colleagues have recently reported that children born prematurely and exposed to repeated painful clinical procedures will demonstrate a deficit of DNIC when tested in later childhood [71].

**Psychologic factors**

Finally, psychologic factors, such as anxiety, depression, and catastrophizing are also important predictors of pain chronicity [74–77]. Psychologic factors will not only predict the reactions to a pain experience or the ability to cope with the pain, but will also affect the evolution of the chronic pain symptoms. The treatment of pain should always take into consideration the role of psychologic factors as an important predictor for a risk of pain chronicity (discussed in the article by Keefe and colleagues in this issue).
Mechanistic approach to pain treatment

Based on the understanding of pain neurophysiology, treatment plans for pain management in the clinical setting may be devised. Treatments could be aimed toward either reducing excitatory mechanisms or enhancing inhibitory activity. The first goal is to identify as best as possible the mechanism’s operative. For a nociceptive acute pain, depending on the nature of the injury, topical or systemic anti-inflammatory (NSAIDs) or analgesic treatments would be primarily indicated. However, even if the nociceptive activity is clearly identified to be peripheral, central sensitization may also have occurred.

Chronic pain is even more difficult to manage because of the complexity of pain mechanisms and the evolution of the pathology over time. As a central component to the pain will almost always be present, the use of opioid, anticonvulsant, or antidepressant drugs could be included in pharmacologic treatment.

Types of pain

The different types of pain may be divided into two categories and five subcategories: nociceptive (somatic, visceral, and inflammatory) and neurogenic (causalgia and functional) [78] (Table 1). A purely psychogenic pain may exist, but this is both rare and controversial because of multiple factors influencing pain perception [79]. Caution is needed before diagnosing isolated psychogenic pain.

Nociceptive pain

Nociceptive pain is generally transitory in response to nociceptive stimuli that could be mechanical, thermal, or chemical. Nociceptive pain plays an important protective role and is normally present for as long as the protection of the organism is necessary. However, in certain situations the pain will persist even after healing of the initial injury. Clinicians are currently unable to predict which patients will develop a persistent pain following an acute pain, such as in the case of postsurgical pain, and several factors are implicated. It is for this reason that early treatment of acute pain is so important in the prevention of chronic pain.

The recommended treatments for nociceptive pain are analgesics, NSAIDs, and sodium channels blockers. Opioids also have an important place in the treatment of acute pain, as peripheral opioid receptors are up-regulated following an inflammatory response [80,81]. Persistent acute pain that may have a nociceptive origin may require treatment strategies similar to those used for neuropathic pain to prevent central sensitization.

It is important to differentiate somatogenic versus viscerogenic nociceptive pain that can, in certain cases, present a comparable clinical picture. It is known that referred pain from the internal organs, such as the gut, liver,
<table>
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<tr>
<th>Type of pain</th>
<th>Characteristics</th>
<th>Mechanisms</th>
<th>Example of pharmacologic treatments</th>
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<tr>
<td>Nociceptive</td>
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<tr>
<td>Somatic (tissue injury)</td>
<td>Superficial (skin) or deep pain (muscle, fascia, tendon)</td>
<td>Mechanical, thermal or chemical stimuli</td>
<td>Acetaminophen, Na⁺ blockers, NSAID, steroids, opioids</td>
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<tr>
<td>Visceral (irritable bowel, cystitis)</td>
<td>Constant or cramping, poor localization. Autonomic responses</td>
<td>Visceral distension</td>
<td>NSAID, antispasmodics</td>
</tr>
<tr>
<td>Inflammatory (musculoskeletal)</td>
<td>Localized or diffuse pain hyperalgesia, allodynia.</td>
<td>Associated with localized inflammation</td>
<td>NSAID, steroids</td>
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<tr>
<td>Neurogenic</td>
<td></td>
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</tr>
<tr>
<td>Causalgia (neuralgia, radiculopathy, CNS lesions)</td>
<td>Spontaneous, paroxysmal pain. allodynia, hyperalgesia.</td>
<td>Peripheral or CNS lesions</td>
<td>Anticonvulsivants, opioids, antidepressants</td>
</tr>
<tr>
<td>Functional (FM, thalamic syndromes, irritable bowel syndrome)</td>
<td>Diffuse deep pain, hyperalgesia, allodynia</td>
<td>Dysregulation of excitatory or inhibitory mechanisms in CNS</td>
<td>Antidepressants, anticonvulsivants, opioids, cannabinoids.</td>
</tr>
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</table>
ovaries, or bladder will induce a pain perception localizing in somatic territories, giving the impression of a purely somatic pain. For example, pain arising in the abdominal cavity can mimic low back pain. Appropriate diagnosis and management is dependent upon understanding the concept of referred pain.

**Inflammatory pain**

Inflammatory pain is associated with the healing process following a lesion. Inflammation is a natural protective reaction of the organism following an injury. Inflammatory substances are released into the periphery by cells in the area of damaged tissue but can also arise from hyperactivity of the nociceptive neurons in the CNS, a phenomenon known as neurogenic inflammation [82]. In that the molecules released during inflammation are pronociceptive, the use of NSAIDs will reduce this nociceptive activity. NSAIDs have well-known peripheral effects, but inhibition of cyclooxygenase can also occur centrally in the spinal cord and the brain, and may thereby participate in reducing neurogenic inflammation [83].

**Neurogenic pain**

Neurogenic pain is defined by the International Association for the Study of Pain as pain arising as a direct consequence of diseases affecting the somatosensory system [84]. The mechanisms involved and treatments are different depending on whether the pain originates peripherally (vascular, mechanical, or chemical lesion affecting the nerve) or centrally (spinal or supraspinal hyperactivity). Neurogenic pain, even of a peripheral origin, is frequently associated with sensitization of the CNS. Pharmacologic approaches to treatment of neurogenic pain aim to reverse or reduce the hyperactivity of the nociceptive neurons. Commonly used agents include opioids, anticonvulsivants, antiarrhythmics, antidepressants, and even NMDA receptor antagonists (e.g., ketamine).

**Functional neurogenic pain**

Functional neurogenic pain is a subcategory of neurogenic pain occurring in the absence of a defined anatomic lesion within the nervous system, but rather representing a dysfunction of pain modulation mechanisms. This may occur as a result of central activation of endogenous excitatory systems that will amplify the nociceptive signal or by a dysfunction of endogenous inhibitory mechanisms.

An example of central hyperactivity is the thalamic syndrome following a lesion of thalamic nuclei as a result of a cerebral event. This lesion will produce hyperactivity of thalamic neurons that are normally inhibited by a complex interneuron network. A small lesion within the thalamus may result in intense pain over a large body area, frequently involving almost half of the body. In contrast, another pain syndrome, namely FM, may be at least partly explained by a deficit of descending endogenous pain inhibitory
mechanisms [25]. In this condition the hyperalgesia is related to lack of inhibition, rather than just hyperactivity of the nociceptive neurons.

Therefore, strategies for the treatment of functional neurogenic pain will be either focused toward reduction of nociceptive hyperactivity or activation of endogenous inhibition. Anticonvulsants will reduce sensory input by effect on ion channels, whereas antidepressant medications will augment inhibition by effect on serotonin and noradrenergic systems.

**Summary of the mechanistic approaches to the treatment of pain**

Based on one’s knowledge of the neurophysiology of pain and the specific mechanisms involved, therapeutic strategies may be selected.

- Nociceptive pain arising in the periphery may be treated by reduction of inflammation (NSAID), blocking the activity of the nerve fibers (ion channels blockers), or by acting on the C-fiber receptors by using an agent such as capsaicin.
- If there is reason to suspect hyperactivity of spinal neurons following a sensitization of the CNS (allodynia, hyperalgesia), then anticonvulsant or antiarrhythmic agents are used to reduce neuronal hyperactivity. NMDA antagonists could also be used to reverse this hyperactivity. It is also possible that the prophylactic use of these agents, such as during surgery, may prevent chronic pain.
- If the descending inhibitory mechanisms are implicated, the use of serotonergic and noradrenergic agonists, as in the antidepressants, may help to recruit and modulate these systems.
- Finally, antidepressant medications, opioids, and the anticonvulsant drugs would also have an effect on the higher centers influencing the motivational aspect of pain.
- Cognitive manipulation can also play a role in pain modulation. Harnessing these mechanisms from higher cerebral centers by use of distraction, relaxation, suggestion, and positive support will facilitate pain management.

These pharmacologic and nonpharmacologic examples, based on the neurophysiologic characteristics of the pain, demonstrate that a better understanding of the mechanisms of pain generation will influence therapeutic approaches and facilitate treatments.

**Summary**

This article has described the complexity of the pain phenomenon and explained mechanisms involved in the development and maintenance of pain conditions. This knowledge is a strong foundation on which to develop a therapeutic guide for the treatment of pain. Although there is commonality in the nociceptive pathways of our patients, each individual will respond
differently to pain as a result of genetic and environmental background. This variability in perception and response to pain may lead to physician bias or even misinterpretation of an individual patient’s symptoms. Keeping in mind the heterogeneity of the pain response and the unique characteristics of an individual patient will lead to better patient care. Understanding the neurophysiologic mechanisms underlying the development and maintenance of pain will help focus treatments more efficiently toward the specific abnormality causing pain. The knowledge of the science of pain has provided an opportunity to address pain from a mechanistic approach, with the objective of reinforcing inhibitory mechanisms or reducing the hyperactivity of the nociceptive response.

References


