Perioperative pain: physiology and pathophysiology

Perioperatieve pijn: fysiologie en pathofysiologie

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ABSTRACT

This review describes the physiology and pathophysiology of perioperative pain in domestic animals. Different definitions of pain, as well as different aspects of the pain experience (transduction, transmission, modulation and perception) are discussed in detail.

SAMENVATTING

In dit overzichtsartikel worden de fysiologie en de pathofysiologie van perioperatieve pijn bij huisdieren beschreven. De verschillende definities van pijn en de verschillende aspecten van pijnervaring (transductie, transmissie, modulatie en perceptie) komen aan bod.

INTRODUCTION

Descartes postulated in the 17th century that animals were *automata* and therefore unable to experience pain. Up through a great part of the 20st century, this theory was unfortunately accepted by science, which meant that few or no analgesics were used in veterinary medicine. Today, most veterinarians have no problem in admitting that animals do experience pain. However, studies evaluating the attitudes of veterinarians in different countries towards postoperative pain suggest that the use of perioperative analgesics is still inconsistent and tends to be low after many surgical interventions (Hewson *et al.*, 2006). One of the possible explanations for the lack of appropriate analgesic treatment could be the inability of veterinarians and veterinary nurses to recognize pain in the wide variety of species referred for treatment. In a questionnaire about analgesia in dogs and cats distributed among French veterinarians, 14.3% of the respondents considered their knowledge of pain recognition to be inadequate, and more than 50% reported that their methods of pain quantification and monitoring were insufficient (Hugonnard *et al.*, 2004). Aside from their inability to recognize pain, veterinarians are often relatively reluctant to use perioperative analgesics, mainly because of a lack of familiarity with the available drugs, major concerns about the side effects, and practical objections relating to the record keeping that is required for controlled substances such as opioids (Lascelles *et al.*, 1999; Muir and Woolf, 2001; Wright, 2002).

Effective management of perioperative pain remains an ethical responsibility for veterinary practitioners. Over the last decade, there has been a renewed awareness of the need for analgesic treatment in animals, together with major scientific advancements in understanding the pathophysiological processes involved in pain transmission (Woolf, 2000). This positive evolution has led to newer theories in the domain of the optimal use of perioperative analgesia. Terms such as “pre-emptive analgesia”, where analgesics are administered before any noxious stimulus occurs (Woolf, 1983; Dahl and Kehlet, 1993; Lascelles *et al.*, 1997; Moiniche *et al.*, 2002), and “multimodal analgesia”, where a cocktail of analgesic drugs with different modes of action are combined (Kaneko *et al.*, 1994; Slingsby and Waterman Pearson, 2001), have emerged and gained interest in daily veterinary medicine. Consequently, it is mandatory that veterinarians become familiar with the physiology and pathophysiology of pain, so they can efficiently select the best “analgesic plan” for each individual patient (Woolf, 2000).

This paper gives an overview of the current definitions of pain and the physiology and pathophysiology of pain.

DEFINITION(S) OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*" (Kelly *et al.*, 2001). Pain requires integration of nociceptive and other sensory information at the cortical level (Lemke, 2004), and is therefore a conscious awareness of acute or chronic discomfort in variable degrees. Pain can be the result of injury, disease, or emotional distress as evidenced by biological and/or behavioral changes. This subjective experience is accompanied by feelings of fear, anxiety, and panic, which elicit protective motor actions, resulting in learned avoidance and possible modification of species-specific behavior (Hellyer et al., 2007). Furthermore, pain is considered to consist of three key components. The sensory-discriminatory component provides information on the onset, location, intensity, type and duration of the stimulus. The motivational-affective component is closely associated with the autonomic nervous system's cardiovascular, respiratory and gastrointestinal changes, and disturbs the feeling of well-being in the individual, thus triggering certain actions in an animal (Hellyer *et al.*, 2007). The magnitude of quality (e.g. stabbing/pounding, mild/severe) has been quantified by the cognitive-evaluative component (Price and Nolan, 2007) and includes also the effects of prior experience, anxiety, attention and conditioning (Hellyer *et al.*, 2007).

Different classifications of pain have been reported in the literature. The classification can be done on the basis of an anatomical (somatic versus visceral pain), a temporal (acute versus chronic pain) or an etiological approach (inflammatory versus neuropathic pain) (Lemke, 2004).

Perioperative pain is probably best divided into two types on the basis of the physiological/adaptive and the pathological/maladaptive concepts (Woolf and Chong, 1993). Physiological pain is defined as the type of pain that is experienced abruptly over a short period of time. It requires a high-threshold noxious input, is well localized and transient, and serves a protective function (Woolf, 2000; Muir and Woolf, 2001; Lemke, 2004). It informs the individual that something "out there" is harmful and needs to be avoided (Woolf, 2000). Pathological or maladaptive pain, on the other hand, is defined as the pain following severe trauma and persisting beyond the usual course of an acute disease or beyond the reasonable time it takes for an injury to heal. Beyond that, this kind of pain can be associated with chronic pathological processes persisting or recurring for months or even years. It requires low-threshold input, results in extended discomfort and abnormal sensitivity and therefore does not have a protective function (Muir and Woolf, 2001; Lemke, 2004; Hellyer *et al.*, 2007). Under clinical conditions, pathological pain has been categorized in terms of the most likely mechanisms responsible, including inflammation and neuropathy. Nerve transection and compression are possible causes of neuropathic pain, whereas surgical procedures, trauma, ischemia, osteoarthritis, infection, and abscessation induce inflammatory pain. On the other hand, head trauma, vertebral disc prolapse, amputation, total ear canal ablation, cancer and some specific inflammatory processes (eg, pancreatitis) can be accompanied by elements of both inflammation and neuropathy (Muir and Woolf, 2001).

Severe injuries and chronic pathological pain states can lower the threshold required to initiate pain: this has been defined as hypersensitivity. Under normal conditions, the main goal of the biological imperative is to assist and repair the healing process after damage of tissues (Woolf, 2000). Hypersensitivity induces the development of exaggerated responses to noxious stimuli, which is defined as hyperalgesia. It can also lead to allodynia, which has been defined as pain arising from normally non-painful perceptions (Muir and Woolf, 2001). The processes of peripheral and central sensitization can explain the physiological background for the occurrence of both hyperalgesia and allodynia. To understand the meaning of these pathophysiological pain terms, basic knowledge of the physiology of pain is essential.

PROCESSES IN THE SENSORY PATHWAY

Transduction, transmission, modulation and perception are the four major processes which are involved in the sensory pathway of pain (Figure 1) (Kelly *et al.*, 2001). The nociceptive pathway is a 3-way neuron chain in its simplest form, in which the first or the primary afferent neuron is responsible for transduction of noxious stimuli and transmission of signals from the periphery to neurons in the dorsal horn of the spinal cord. Modulation of the signal takes place at the spinal level. The second or the projection neuron receives input from the first neurons and projects the signal to neurons in higher centers of the brain (medulla, pons, midbrain, thalamus and hypo-

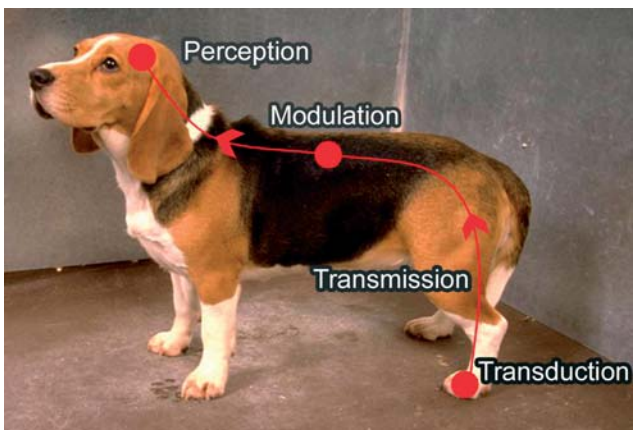

Figure 1. Schematic representation of the processes in the sensory pathway. The arrows indicate the afferent direction of pain signaling.

thalamus). In these centers, third order supraspinal neurons integrate signals from the spinal neurons and project them to subcortical and cortical areas where pain is finally perceived (Lemke, 2004).

Transduction

Nociception is the neurophysiological process whereby noxious thermal, chemical or mechanical stimuli are transduced into action potentials by high-threshold pain receptors, defined as nociceptors (Kelly *et al.,* 2001; Muir and Woolf, 2001; Lemke, 2004). Nociception provides information about the state of the environment near the individual and relays it to the central nervous system (CNS). The encodement of the noxious stimulus by the nerve endings of afferent sensory pain fibers is based on the modality, intensity, duration and location of the stimulus, with intensity being the most important factor for the final determination of the severity of pain (Muir and Woolf, 2001).

The primary afferent nociceptors are the distal terminals of the Ad and C nerve fibers, the cell bodies of which are located in the dorsal root ganglia on the dorsal root of the spinal nerves originating in the body. For the trigeminal, facial, glossopharyngeal and vagus nerves originating from the head, the cell bodies are located in the trigeminal ganglia (Woolf, 2000; Kelly *et al.,* 2001; Muir and Woolf, 2001). Each nociceptor can specifically detect a particular type of stimulus such as touch, temperature, pain, etc. Receptors are distributed in skin and deep tissues in varying densities.

Four classes of nociceptors have been described up to now. Mechanical nociceptors respond to intense pressure and thermal nociceptors respond to extreme temperatures; these two types of nociceptors have been classified together as Ad mechano-thermal nociceptors (Lemke, 2004). Polymodal nociceptors respond to noxious chemical, mechanical and thermal stimuli (Raja *et al.,* 1988; Basbaum and Jessel, 2000; Hellebrekers, 2000). Schaible and Schmidt (1983) reported that many nociceptors, and most likely all of them, are inactive and rather unresponsive under normal circumstances. These silent or sleeping nociceptors are activated by inflammatory mediators and only respond to mechanical and thermal stimuli when activated (Schaible and Schmidt, 1985; Greenspan, 1997; Willis and Westlund, 1997; Basbaum and Jessel, 2000; Hellebrekers, 2000).

Transmission

After transduction, the electrical stimulus generated must be transmitted to superficial and deeper layers of the dorsal horn of the spinal cord. Nociceptors that respond to thermal or mechanical stimuli transmit their information through large diameter, myelinated Aδ nerve fibers. These have a high threshold and high conductive speed (5-30 m/s) and are related to "first" pain, which is defined as sharp, prickling and injurious pain. The signals of polymodal and silent nociceptors are transported by small diameter, unmyelinated, slowly conducting (0.5-2 m/s) C nerve fibers. These fibers are responsible for "second" pain, which is characterized by the occurrence of dull, aching and visceral pain (Basbaum and Jessel, 2000; Hellebrekers, 2000; Kelly *et al.*, 2001; Lemke, 2004; Price and Nolan, 2007). Both types of nociceptive fibers innervate the skin (superficial pain) and deep somatic or visceral structures (deep pain) (Hellyer *et al*, 2007). A third class of nerve fibers, the Aβ-fibers, are activated by low threshold stimuli such as touch, which normally leads to an innocuous sensation (Hellebrekers, 2000). However, in cases of peripheral sensitization, they will contribute to the transmission of pain signals (Price and Nolan, 2007). This will be further explained under the item peripheral sensitization.

A variety of neurotransmitters, including excitatory amino acids (glutamate and aspartate), the neuropeptides (substance P and neurokinin A) and calcitonin gene-related peptide (CGRP), are released by the first order neuron after stimulation (Kelly *et al.*, 2001; Lemke, 2004). Normal afferent input results in the release of glutamate, which binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Lemke, 2004) and kainate ligand-gated ion channels (Woolf and Salter, 2000). The binding of glutamate on the AMPA receptor generates fast post-synaptic potentials, which last for milliseconds. The neuropeptides bind to neurokinin receptors (Lemke, 2004). N-methyl-D-aspartate (NMDA) ion channels (receptors) remain blocked by magnesium ions (Mg^{2+}) under normal conditions (Muir and Woolf, 2001).

Nociceptive fibers synapse with second order nociceptive neurons in the dorsal horn of the spinal cord. They enter the grey matter of the spinal cord using the so-called "Lissauer's tract", which is a dense system of predominantly propriospinal fibers extending longitudinally from the periphery of the dorsal horn to the cord's surface (Fine and Ashburn, 1998). The grey matter of the spinal cord can be divided into layers, which were initially described in the cat (Rexed, 1954) and are called "Rexed laminae" (Figures 2 and 3). They consist of functionally distinct cells that form columns extending over the length of the spinal cord. The borders between these laminae are not clearly separated, so an overlap is present. Aδ-fibers synapse in laminae I, II and V, while C-fibers connect in laminae II, the so-called substantia gelatinosa (Kelly *et al.*, 2001; Muir and Woolf, 2001; Price and Nolan, 2007) and send branches to laminae I en V (Fine and Ashburn, 1998; Muir and Woolf, 2001; Lemke, 2004). The large Aβ sensory nerve fibers terminate on neurons located in laminae III, IV and V, which project sensory information to the brain and integrate sensory input with descending information from the brain (Doubell *et al.*, 1999).

Three types of second order neurons, the projection

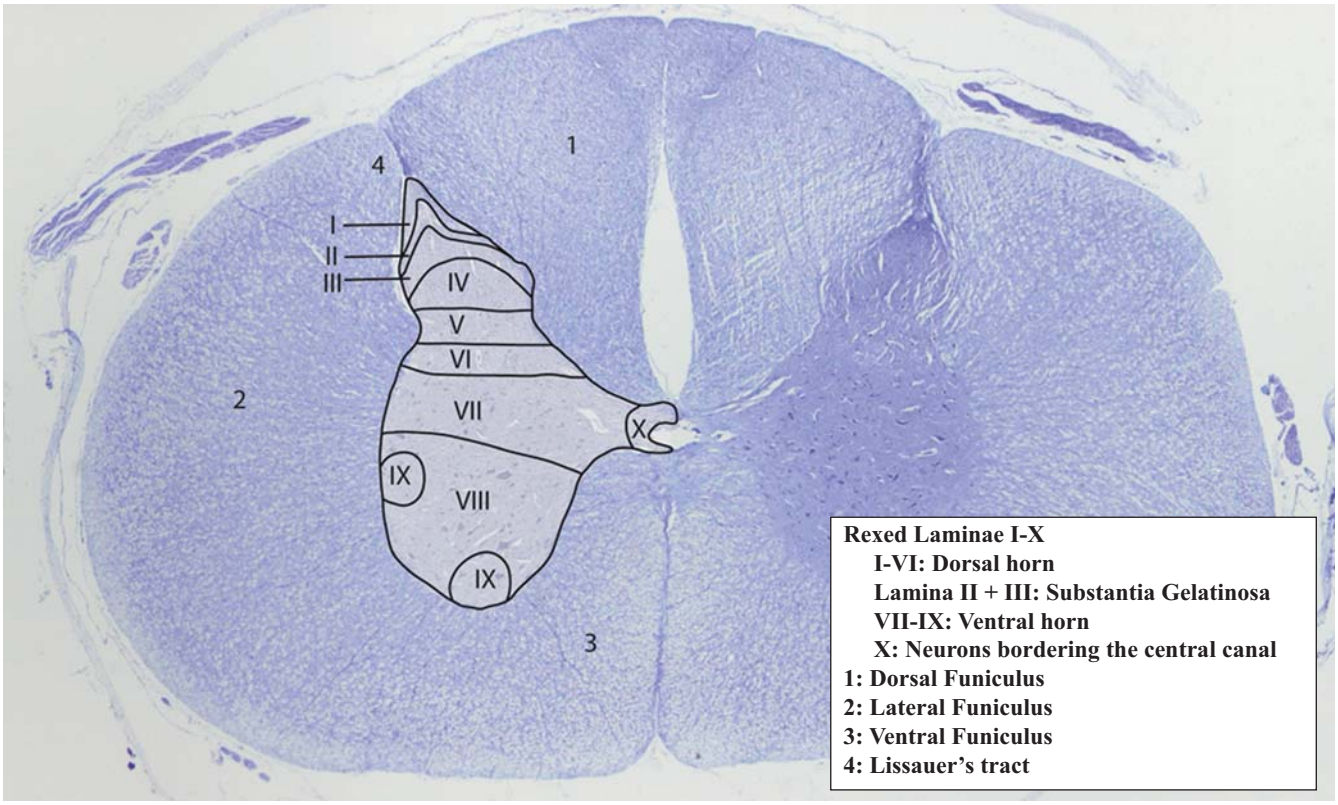

Figure 2. Cross section of the second cervical spinal cord segment of a cat on which a schematic representation of the Rexed Laminae is projected (Nissl stain, x4).

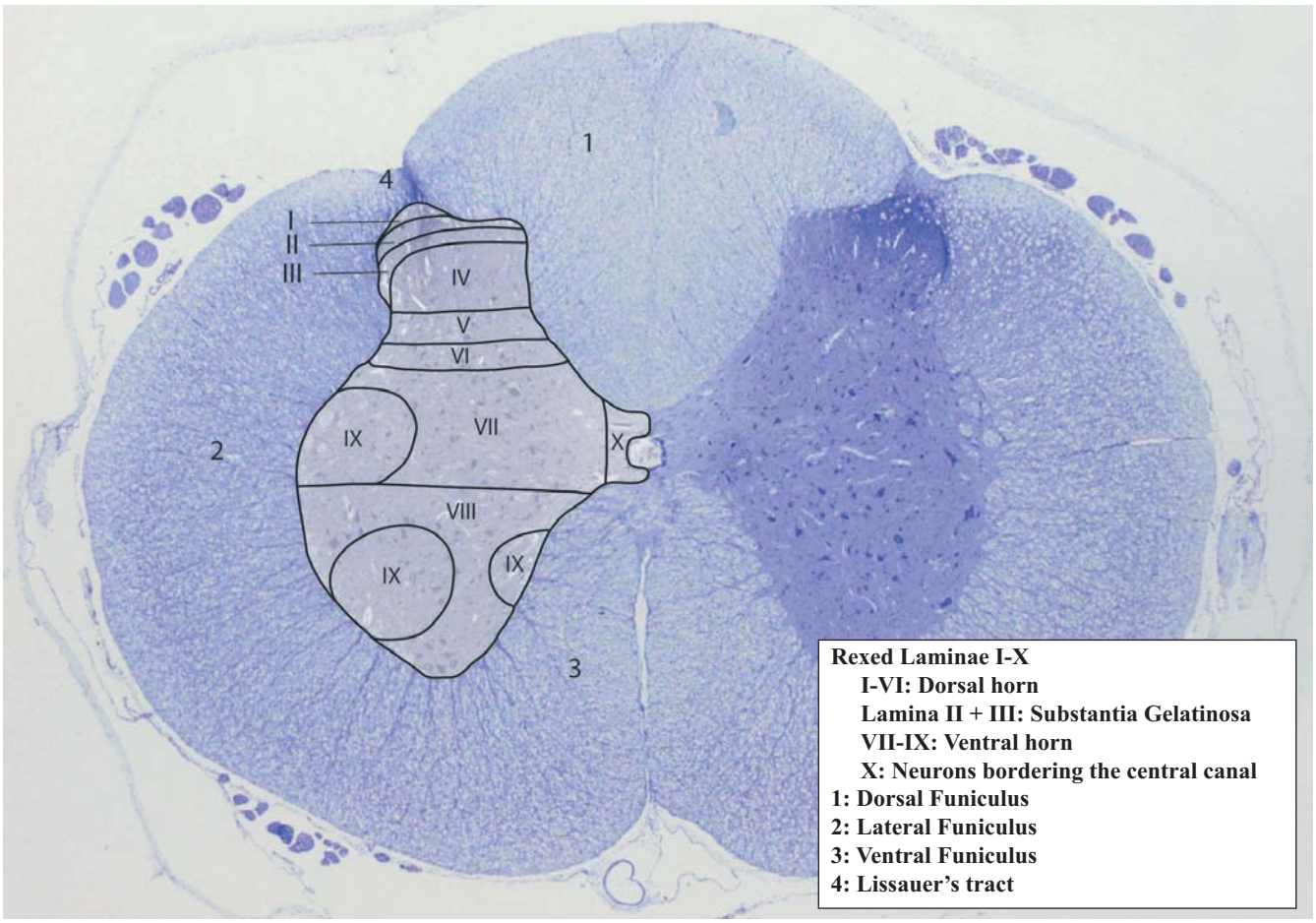

Figure 3. Cross section of the fourth lumbar spinal cord segment of a cat on which a schematic representation of the Rexed Laminae is projected (Nissl stain, x4).

neurons, interneurons and propriospinal neurons, have been described in the dorsal horn. Two distinct types of projection neurons are primarily responsible for the further signaling of pain sensations to supraspinal third order neurons (Dahl and Moiniche, 2004). Projection neurons in lamina I receive input directly from nociceptive Aδ- and C-fibers and are therefore defined as Nociceptive Specific (NS) neurons. Other neurons, which are mainly located in lamina V but also in laminae I and II (Jänig, 1987), receive nociceptive and non-nociceptive (Aβ-fibers) information and were classified as Wide Dynamic Range (WDR) neurons (Dahl and Moiniche, 2004; Lemke, 2004). A WDR neuron has a typical large receptive field with a central area responsive to noxious and tactile stimuli (Aβ-fibers), while the periphery is responsive only to noxious stimuli (Mendell, 1966; Fine and Ashburn, 1998; Lemke, 2004). Its activity is determined by the balanced total effect of excitatory and inhibitory inputs from their respective peripheral nerve fibers, local circuit excitatory and inhibitory neurons, and descending inputs from supraspinal sites (Dahl and Moiniche, 2004).

The columns also contain a large number of second order excitatory and inhibitory interneurons (lamina II) that receive nociceptive and non-nociceptive multiple inputs from surrounding columns and send outputs to the brain and the ventral (motor) horn (Rexed, 1952). They play a key role in gating and modulating nociceptive input (see central sensitization) (Lemke, 2004).

Propriospinal neurons extend over several spinal segments and are responsible for segmental reflexes associated with nociception (Lemke, 2004).

Modulation/Modification of pain

Somatosensory pathways cannot be conceived of as “hard wired” electrical circuits that respond to stimuli in predictable ways and consistently produce a sensory perception in accordance with the stimulus in the periphery (Hellyer *et al.*, 2007). On the contrary, pain is an active process generated partly in the periphery and partly in the central nervous system by multiple plastic changes that determine the gain of the system (Woolf and Salter, 2000). Nociceptive signals will rather launch a cascade of alterations (modulations) in the somatosensory system. This can take place in the periphery, the spinal cord, the brain stem and in higher centers (Woolf and Salter, 2000; Hellyer *et al.*, 2007). Alterations in the somatosensory system have been defined by Woolf and Chong (1993) as neural plasticity or the ability of the nervous system to modify its function in response to different environmental stimuli (Lemke, 2004).

The plasticity responsible for clinical pain hypersensitivity has two general forms, namely modulation and modification. Modulation represents posttranslational reversible changes in the excitability of neurons through the phosphorylation of receptor / ion channels, or associated regulatory proteins, resulting in altered intrinsic functional properties or cell-surface expression of channels in primary sensory and dorsal horn neurons. Modification stands for long lasting changes in the expression of transmitters / receptors / ion channels (Woolf and Salter, 2000), such that alterations in patterns of gene expression can occur, changing the phenotype of neurons (Muir and Woolf, 2001). As a result, the normal stimulus-response characteristics will be distorted (Woolf and Salter, 2000).

Surgical procedures will induce tissue damage and injury of nerve fibers. When there is limited perioperative tissue trauma and inflammation, the pain will be discrete, proportionate and protective. It will resolve once the inflammatory response has subsided (see definition of physiological pain). In contrast, extensive or chronic trauma, inflammation and neuropathic pain (nerve damage) will induce varying degrees of peripheral and central sensitization, so the animal will experience pain that is diffuse, disproportionate and debilitative, and which continues beyond the resolution of the inflammatory process (see definition of pathological pain) (Lemke, 2004).

Peripheral sensitization

Peripheral sensitization is caused by the increased sensitivity of the nociceptors resulting from extensive trauma and inflammation (Raja *et al*., 1988). In the initial stages of inflammation, this will result in a decrease in pain threshold, a subsequent exaggerated response to noxious stimuli, and often spontaneous pain at the site of injury (Kelly *et al.*, 2001; Muir and Woolf, 2001). This phenomenon is defined as *primary* hyperalgesia (Raja *et al*., 1988; Levine *et al.*, 1993; Muir and Woolf, 2001), whereas *secondary* hyperalgesia refers to changes in the area surrounding the tissue injury (Raja *et al.*, 1988). The latter changes cannot be explained by peripheral sensitization, because no change in nociceptor transduction was found outside the area of primary hyperalgesia (Muir and Woolf, 2001). Peripheral sensitization will also lead to a reduction in the intensity of the stimulus necessary to initiate pain, so stimuli that would normally not cause pain begin to do so (allodynia) (Muir and Woolf, 2001; Muir, 2007).

Translated to the cellular level, this means that trauma leads to the release of sensitizing chemical mediators from inflammatory cells. Neutrophils, macrophages and lymphocytes produce cytokines (interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)-α) (Muir, 2007). Mast cells degranulate with a release of histamine and serotonin (5-HT). Histamine stimulates the sensory neurons, causing pain and itching; it can evoke the release of other neuropeptides and prostaglandins, leading to an acceleration of the inflammatory process (Kelly *et al.*, 2001). Serotonin, which is released by mast cells and platelets, plays a role in the early phases of some types of acute

inflammatory responses (Garcia Leme *et al.*, 1973). Bradykinin's induction of sensitization is largely dependent on prostaglandin synthesis, but it can also activate nociceptors directly (Levine *et al.*, 1993). It has pro-inflammatory functions, including the release of prostaglandins, cytokines and free radicals, and the degranulation of mast cells (Kelly *et al.*, 2001). Damaged cells release potassium ions and adenosine triphosphate, but they also produce cyclo-oxygenase-2 (COX-2) in inflammatory cells, leading to the production of prostaglandins and leukotrienes, possibly in the nerve terminals themselves (Vane *et al.*, 1998; Muir, 2007). These inflammatory mediators cause further sensitization of the peripheral receptors, thereby reducing their activation threshold and increasing the responsiveness to other stimuli (Levine *et al.*, 1993). Neurotrophic factors (NGF's), which are released during tissue damage or by inflammatory cells, sensitize the transducers to subsequent stimuli (Woolf and Salter, 2000). Nociceptive input will activate the sympathetic nervous system, resulting in the release of norepinephrine, which in turn accelerates sensitization of the nociceptors (Dray, 1995; Dahl and Raeder, 2000; Hellebrekers, 2000; Kelly *et al.,* 2001). Stimulation of nociceptors also leads to antidromal (reverse) activation of nociceptive nerve terminals and subsequent release of the neuropeptides CGRP and substance P. These neuropeptides, together with proteases, induce mast-cell degranulation, vasodilatation and edema, as well as further activation of nociceptors and adjacent sensory nerve fibers (neurogenic inflammation). This will lead to hypersensitivity of the non-injured surrounding tissue, which is defined as secondary hyperalgesia (Hellebrekers, 2000; Kelly *et al.*, 2001; Muir, 2007).

In the end, the free nerve endings of the nociceptive afferents will be "bathed" in an environment of inflammatory mediators, the so-called "inflammatory soup". This "soup" consists of the above described vasoactive amines, ions, neuropeptides and different products of the arachidonic acid cycle (Hellebrekers, 2000).

In conclusion, both neural and non-neural cellular elements are necessary for different mediators to act upon primary afferent nociceptors. Some of these mediators directly sensitize these nociceptors, while others act on cells other than the nociceptors, which in turn release a hyperalgesic agent that acts directly on the primary afferent nociceptor (Levine *et al.*, 1993).

Central sensitization

The IASP defines central sensitization as "*an enhanced responsiveness of nociceptive neurons in the central nervous system to their normal afferent input*". These nociceptive neurons have very distinct and even antagonistic functions, not all of which are related to the perception of pain. They may also project to different areas in the brain and to motoneurons or may be interneurons. Enhanced responsiveness of different nociceptive neurons may have distinct and perhaps opposing consequences in terms of pain. Consequently, central sensitization may lead to hyperalgesia and/or allodynia, while on the other hand it may also lead to stronger feedback inhibition or endogenous pain control (Sandkühler, 2007).

Sensory homeostasis is maintained within the spinal cord by a balance between neural inputs and descending excitatory and inhibitory influences from the brain. The "gate control theory", first proposed by Melzack and Wall (1965), suggested that low-threshold Aβ-fibers and high-threshold C-fibers modulate the activity of inhibitory interneurons located in the spinal cord. Activation of the low-threshold Aβ-fibers, which normally transmit innocuous stimuli, increases inhibitory interneuron effects (Hellyer *et al.*, 2007; Muir, 2007) by inducing both tonic and phasic inhibitory effects upon nerve impulses and their projection to the brain (Gjerstad *et al.*, 2001). The inhibitory action is mediated by gamma-aminobutyric acid (GABA) and glycine acting on $GABA_A$ and $GABA_B$ receptors (Yaksh, 1989; Woolf and Salter, 2000). Activation of Aδ-fibers and C-fibers results in inhibition of the inhibitory interneurons (Muir, 2007). Many contemporary pain researchers object to the continued use of the term "gate control theory" (Hellyer *et al.*, 2007).

Another modulation model is the "Diffuse Noxious Inhibitory Control" (DNIC) concept. This concept is based on counterirritation, where one painful stimulus reduces the pain caused by a concurrent noxious stimulus somewhere else in the body (Talbot *et al.*, 1989). For example, pain induced by intraneural electrical stimulation at C-fiber strength can be substantially reduced by vibration of the skin within the projected pain region (Bini *et al.*, 1984). The mechanism of DNIC involves inhibition of the activity of WDR neurons in the dorsal horn (Chapman and Nakamura, 1999).

Various neuromodulators can adapt the excitatory and inhibitory synaptic transmission in the spinal cord. GABA, opioids, serotonin and norepinephrine inhibit excitatory transmission, while ATP, substance P, and prostanoids facilitate the excitatory transmission. On the other hand, serotonin, norepinephrine and acetylcholine facilitate inhibitory synaptic transmission (Muir, 2007).

As stated before in the discussion of transmission in the dorsal horn, normal afferent input will induce the release of glutamate, which binds to AMPA receptors. Glutamate's action on the AMPA receptor is responsible for the generation of fast excitatory post-synaptic potentials (EPSP's), which last for milliseconds. These potentials signal the onset, duration, intensity and location of the stimulus (Duggan *et al.*, 1990). Central excitatory sensitization will occur when the repetitive thermal or mechanical stimulation of peripheral nociceptors (partially dependent on the development of peripheral sensitization) continuously stimulates neurons in the dorsal horn of the spinal cord, resulting

in temporal summation and cumulative depolarization of dorsal horn neurons (Woolf and Thompson, 1991). This leads to the sustained release of glutamate, substance P and the Brain Derived Neurothrophic Factor (BDNF) (Lemke, 2004; Hellyer, 2007), which will then produce slow EPSP's lasting for tens of seconds (Thompson *et al.*, 1990). When substance P is released from high-threshold fibers, CGRP is released simultaneously, which in turn extends the spinal cord zone from which substance P is released (Skofitsch and Jacobowitz, 1985). This phenomenon contributes to the increased excitability (Schaible *et al.*, 1994) and activation of additional types of glutamate receptors such as N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors (mGluR), resulting again in enhanced synaptic transmission (Muir and Woolf, 2001; Lemke, 2004). The magnitude of these events is proportional to the stimulus intensity and is responsible for the removal of magnesium blocking the NMDA receptor. Consequently, a prolonged enhancement of dorsal horn neurons to glutamate or NMDA will occur (Willcockson *et al.*, 1984; Dougherty and Willis, 1991; Muir and Woolf, 2001), which causes calcium influx into postsynaptic neurons, followed by persistent changes in the excitability of the neuron (Dray, 1995). The whole of NMDA receptor activation (i.e. making it more available for activation by glutamate through the removal of the magnesium block) and the increased excitability of projection neurons is called "*wind-up*", which is supposed to be the physiological trigger for central sensitization (Woolf, 1996; Muir and Woolf, 2001). This is fundamentally different from peripheral sensitization because central sensitization enables low-intensity stimuli to produce pain sensations (Muir and Woolf, 2001). This mechanism also allows Aβ-sensory fibers to induce pain by altering spinal cord sensory processing and increasing spinal neuron excitability (Baba *et al.*, 1999).

ASCENDING SPINAL PATHWAYS

After modulation of the nociceptive signal in the dorsal horn of the spinal cord, the signal is further projected through ascending pathways to higher centers (Figure 4: localization of centers), where conscious and subjective perception of the stimulus takes place as a result of successful transduction, transmission and modulation of the signal (Muir and Woolf, 2001). The white matter of the spinal cord of domestic mammals is organized in functional tracts (Figure 5). Among these tracts, there are multiple nociceptive pathways. None of these is exclusively involved with pain transmission, and all have fibers conducting tactile information (Hellyer *et al.*, 2007). Spinal pain pathways also differ between animal species, but the common ones include the spinothalamic, the spinoreticular and the spinomesencephalic pathways.

Spinothalamic pathway

The spinothalamic pathway is considered important for the transmission of deep pain and temperature (Burke and Colter, 1990). It originates from laminae I and IV to VII of the spinal cord and contains axons of NS and WDR neurons (Muir, 2007). These are distributed to the lateral funiculus on both sides of the spinal cord, forming a bilateral pathway (Figure 5). They may re-enter the grey matter and make synapses with new neurons. The axons of these new neurons return to the spinothalamic tract either on the same or on the other side of the spinal cord. This means that the spinothalamic pathway in domestic mammals is both crossed and uncrossed, and that it is multisynaptic with multiple interruptions (Kennard, 1954; King, 1987; Thomson, 2006). It is also connected with the propriospinal system (King, 1987).

There is a huge difference between the spinothalamic pathway anatomy of animals and of humans. In humans, all ipsilateral axons are projected across the midline and ascend in the contralateral spinothalamic tract uninterrupted to the reticular formation or the thalamus. Hemisection of the cord in man causes contralateral loss of pain and temperature sensation distal to the level of the lesion. Animals do not demonstrate such contralateral hemianalgesia. One can understand now why a loss of deep pain sensation conveys a grave prognosis in animals, since deep pain is the product of a diffuse and resilient system, which is difficult to disturb (Burke and Colter, 1990).

The spinothalamic pathway is further divided into medial and lateral components (Figure 4). The medial component projects to medial thalamic nuclei and then, via third order neurons, to the limbic system, and it is responsible for the transmission of ascending nociceptive input involved with the affective-motivational aspect of pain. On the other hand, the lateral component projects to lateral thalamic nuclei and then to the somatosensory cortex. It is responsible for the transmission of nociceptive input involved with the sensory-discriminative aspect of pain (Lemke, 2004).

Of special importance in carnivores is the spinocervicothalamic pathway, which is believed to be the primary conscious pain pathway in these species (Kennard, 1954; Ha and Liu, 1966). This pathway is responsible for the transmission of superficial pain and tactile sensations (Ha and Liu, 1966) and exhibits a high degree of somatotopy, enabling the animal to precisely determine the location of the painful stimulus (Hellyer *et al.*, 2007). Secondary afferents (starting from the dorsal horn) run in an ipsilateral tract and project to and synapse in the lateral cervical nucleus located in spinal cord segments C_1 and C_2. The fibers originating from the cervical nucleus decussate and project to the thalamus. Some collaterals will terminate in the formatio reticularis. Finally, fibers project from the thalamus to the somatosensory cortex (Hellyer *et al.*, 2007).

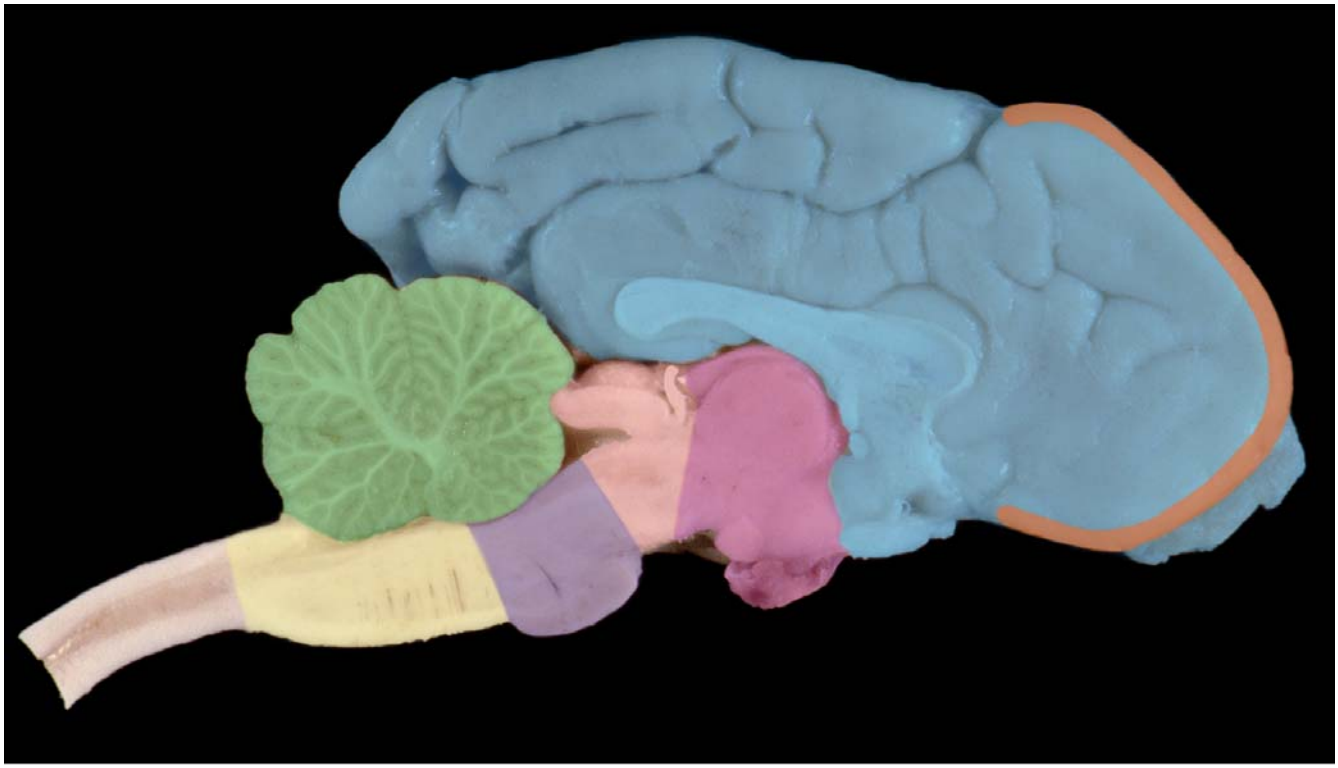

Figure 4. Median section of the canine brain (medial view of the left half of the brain).

Telencephalon

Somatosensory cortex

Cerebellum

Diencephalon: contains Thalamus, Hypothalamus, Hypophysis and nuclei of Formatio Reticularis (FR)

Mesencephalon: contains Substantia Grisea Centralis (Periaquaductal Grey) and nuclei of FR

Metencephalon: contains Locus ceruleus and nuclei of FR

Medulla oblongata: contains Nucleus raphe magnus and nuclei of FR

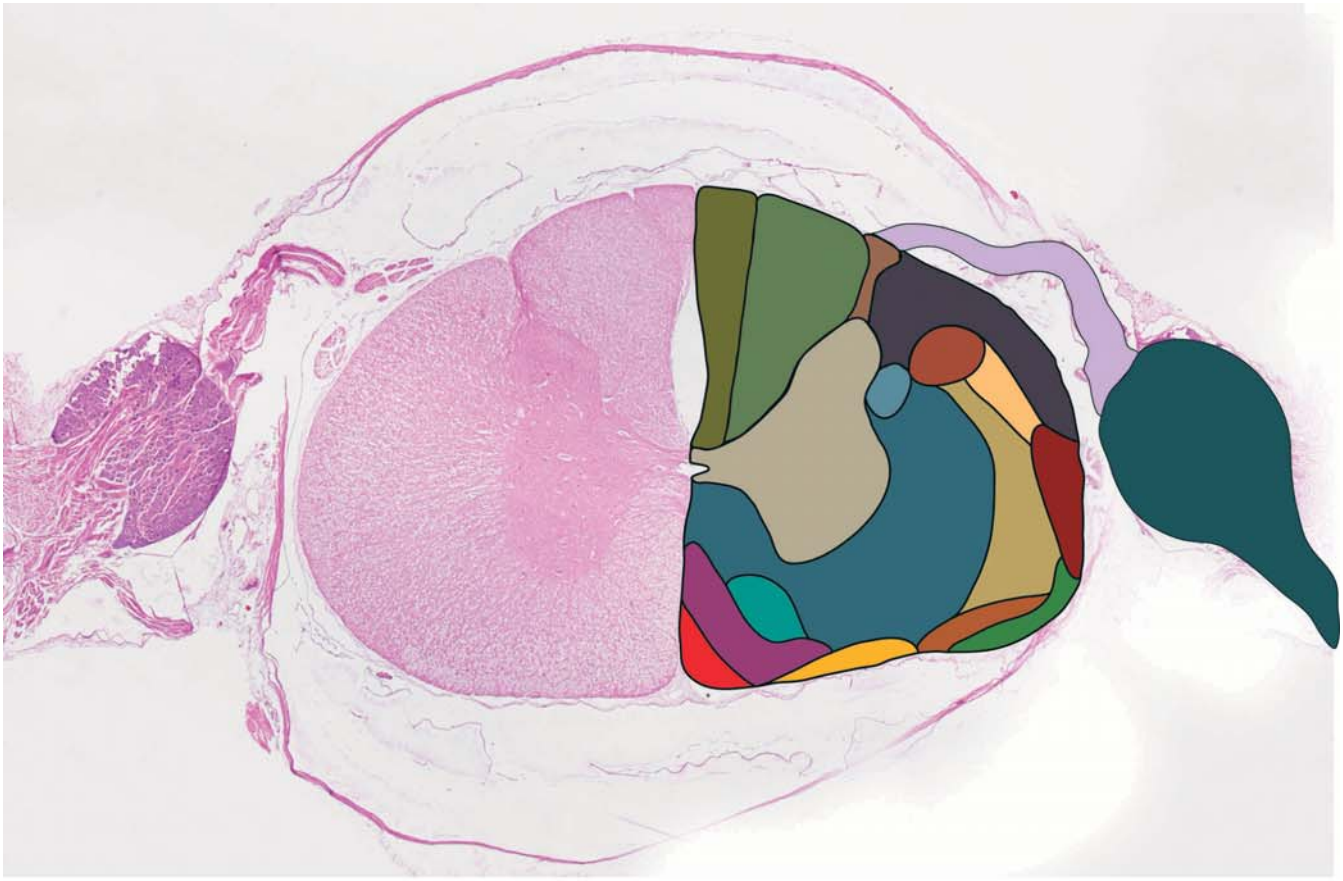

Figure 5. Topography of the main tracts within the white matter of the feline spinal cord at the level of the second cervical segment (HE stain, x 4).

- Gray matter
- Dorsal root ganglion
- Sensory input via dorsal root
- Fasciculus gracilis
- Fasciculus cuneatus
- Dorsolateral tract (Tract of Lissauer)
- Tractus spinocerebellaris dorsalis
- Tractus spinocerebellaris ventralis
- Tractus spinocerebellaris rostralis
- **Tractus spinothalamicus (lateral part)**
- **Tractus spinothalamicus (medial part)**
- **Tractus spinoreticularis**
- Tractus pyramidalis (Tractus corticospinalis lateralis)
- Tractus rubrospinalis
- Tractus spinocervicalis
- Fasciculus proprius
- Fasciculus longitudinalis medialis
- Tractus vestibulospinalis
- Tractus spinoolivaris

Spinoreticular pathway

The primary afferents of the spinoreticular pathway diverge immediately after entering the spinal cord, sending collaterals into several segments rostral and caudal to the segment of entry. This is necessary to participate in intersegmental reflexes. Second-order neurons are located in the dorsal horn and their axons are bilateraly present in the lateral and ventral funiculi (Figure 5). These axons decussate diffusely throughout the long axis of the spinal cord (Hellyer *et al.*, 2007). The spinoreticular pathway projects to the formatio reticularis in the medulla and pons, which is critical for the integration of nociceptive input and is mainly responsible for the transmission of deep pain and visceral sensations (Milne *et al.*, 1981; Ammons *et al.*, 1985; Lemke, 2004; Price and Nolan, 2007). For this reason, somatotopy is not well defined in this pathway (Lemke, 2004). Some ascending projections go directly to the thalamus and then to the cortex, but most projections of deep pain arrive in the somatosensory cortex via diffuse reticular projections to the thalamus (Hellyer *et al.*, 2007). Ascending information increases cortical activity and activates the limbic system, which is associated with emotional responses to pain in humans and determines the aversive quality of the pain experience (Chapman, 1996; Lemke, 2004; Hellyer *et al.*, 2007). Descending reticular activity blocks other sensory activity. There is also a direct link between reticular arousal centers and the dorsal horn (Fine and Ashburn, 1998).

Spinomesencephalic pathway

After synapsing within the superficial layers of the dorsal horn (laminae I and V) (Muir, 2007), axons of the spinomesencephalic pathway decussate and are situated on the contralateral side of the spinal cord (Livingston and Chambers, 2000). They project to the formatio reticularis and the periaqueductal grey matter (PAG) (midbrain). The PAG plays a central role in the integration and modulation of pain at the supraspinal level (Lemke, 2004). These axons also project to the limbic system and the hypothalamus (Muir, 2007). It is possible that the spinomesencephalic pathway activates a system of descending pain inhibition, beginning at the PAG (Fine and Ashburn, 1998).

Spinohypothalamic pathway

This smaller tract projects to autonomic control centers in the hypothalamus and is responsible for the transmission of nociceptive input involved with cardiovascular and neuroendocrine responses to noxious stimuli. It probably mediates some of the autonomic changes in heart rate, arterial blood pressure and respiratory rate in anaesthetized animals undergoing surgery (Lemke, 2004). This is explained by the fact that injury to the body activates the sympathetic nervous system via the hypothalamus (Chapman and Nakamura, 1999).

DESCENDING SPINAL PATHWAYS

Descending antinociceptive pathways begin at the supraspinal level and project to neurons in the dorsal horn of the spinal cord (Fine and Ashburn, 1998; Lemke, 2004). The most important descending system appears to begin in the PAG situated in the midbrain (Basbaum and Fields, 1984; Lemke, 2004). These neurons receive direct input from the thalamus, hypothalamus and reticular formation and indirect input from the cerebral cortex (Basbaum and Fields, 1984; Willis and Westlund, 1997; Lemke, 2004; Hellyer *et al.,* 2007). Some neurons in the mesencephalic PAG project directly to the spinal cord (Castiglioni *et al.*, 1978), but most of the connections are indirect, projecting to the midline nucleus raphe-magnus (rostroventral medulla) and then to neurons in the dorsal horn (Cameron *et al.*, 1995; Fine and Ashburn, 1998; Lemke, 2004). The PAG may also send input to the locus ceruleus (pons) (Cameron *et al* 1995), and the locus ceruleus also projects directly to dorsal horn neurons (Lemke, 2004). Descending axons from neurons in the brain synapse with opioid-containing inhibitory interneurons (Muir, 2007). Axons that originate in the nucleus raphe-magnus release serotonin in the dorsal horn and comprise the "*serotonergic*" pathway. However, axons that originate in the locus ceruleus release norepinephrine in the dorsal horn and comprise the "*noradrenergic*" pathway (Lemke, 2004). Axons of both pathways synapse in the dorsal horn with opioid-containing (endorphin, enkephalin, and dynorphin) interneurons. Activation of these antinociceptive pathways by the supraspinal release of opioid peptides is thought to be responsible for "*stress-induced analgesia*". Inhibition of these pathways is caused by the supraspinal release of gamma-aminobuteric acid (GABA) (Lemke, 2004; Muir, 2007). Paradoxically – and more important in chronic pain states –, release of the opioid peptides inhibits the GABA-mediated inhibition of the antinociceptive pathways, leading to local disinhibitory effects and a potential increase in pain perception (Lemke, 2004; Muir, 2007).

In summary, descending fibers that modulate nociception occur at various sites throughout the central nervous system. The most important inhibitory pathways appear to be serotonergic and noradrenergic and originate in the PAG, which relays through medullary reticular nuclei to the dorsal horn (Fine and Ashburn, 1998).

CONCLUSION AND CLINICAL RELEVANCE

It seems clear now that non-elective surgery patients, with extensive tissue trauma and inflammation present for many days, will show a "pathological" response to pain. In the end, central

sensitization increases the responsiveness of dorsal horn neurons to sensory inputs (allodynia), expands the receptive field, and is believed to be responsible for the discomfort and agony produced by severe injury (Muir and Woolf, 2001). Furthermore, it can lower the threshold for perception of pain with future injuries.

Chronic pain, inflammation and neuropathic pain require a more aggressive and tailored analgesic therapy. Therefore, it is important for practitioners to closely examine each patient before surgery, to establish the degree of expected inflammation and peripheral and central sensitization, before setting up an analgesic plan to treat the patient.

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