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Pain Management in Small Animals Mini Series

Session One: Pathophysiology of Acute Pain and Underpinning Principles of Pain Management

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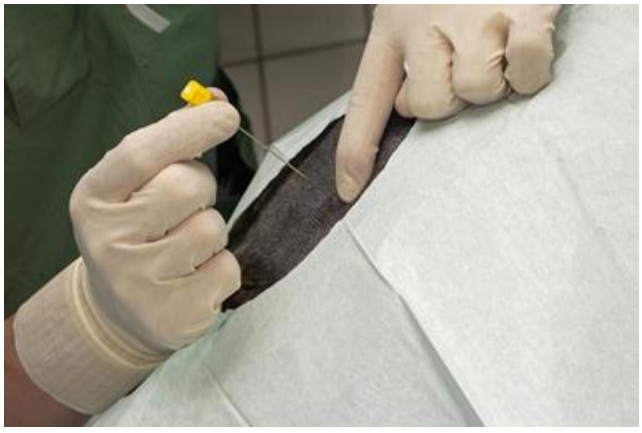

Pain can be classified in a number of different ways. **Acute or chronic** refers to the duration of pain, although there is no universal definition for a time period when acute pain becomes chronic. However the descriptor of **chronic pain is often used when pain outlasts the period of tissue healing**. Clinical pain is used to describe pain that results from tissue injury once modulation of the pain pathways has occurred whereas nociceptive pain describes perception of acute noxious stimuli in the absence of modulation or sensitization of pain pathways. Clinical pain is usually sub-divided into **neuropathic** and **inflammatory** pain. **Inflammatory pain** results from inflammatory processes and may be acute or chronic, whereas **neuropathic pain** results from damage to the nervous tissue itself and is usually chronic in nature.

Visceral or somatic (cutaneous) pain is defined by the type of tissue that is the source of pain. Our understanding of acute somatic pain has grown significantly over the last decade and the expanding use of advanced genetic, molecular, electrophysiological, pharmacological and imaging techniques has led to an increase in knowledge about both functional and anatomical aspects of the pain pathways. Knowledge of visceral and neuropathic pain mechanisms is also growing, but lags behind our understanding of somatic pain. This can be attributed in part to difficulties associated with studying visceral and neuropathic pain systems, including those associated with reliably stimulating visceral organs or inducing neuropathic pain in animal models in a manner that resembles the underlying aetiology of clinical neuropathic pain states.

Nociception or pain?

It is important to distinguish between nociception and pain. **Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage", with the note that the inability to express pain verbally does not negate the possibility that an individual is experiencing pain.** In contrast, nociception is defined as the encoding and processing of noxious stimuli (stimuli that are damaging to normal tissues). Nociception will occur during surgery in animals that are adequately anaesthetized, even though pain will not be present due to the lack of conscious perception provided that the animal is adequately anaesthetised.

Cutaneous pain pathway

The cutaneous pain pathway begins with nociceptors that are located in the skin and detect noxious stimuli in the environment and ends in pain perception due to processes occurring in the cerebral cortex. Information related to noxious environmental stimuli is transduced by nociceptors and transmitted via primary afferent sensory fibers to the dorsal horn of the spinal cord. The signal is then relayed via ascending pathways in the spinal cord to the brain stem and thalamus and finally the cerebral cortex.

Nociceptors

Nociceptors are the free nerve endings of sensory fibers that fire when subjected to stimuli that are of sufficient magnitude to be damaging to tissue. Different nociceptors that respond to different types of noxious stimuli have been characterized using electrophysiological techniques. Nociceptors that are associated with myelinated A δ fibers mediate acute, well localized, fast pain; in effect the onset of pain perception associated with a particular stimulus, whereas unmyelinated C fiber nociceptors mediate slow poorly localized "second pain". A δ nociceptors are divided into two types, type I and type II. Type I A δ nociceptors (ATM's) are described as high threshold mechanical receptors that respond primarily to mechanical and chemical stimuli, although they are also activated by heat at high temperatures (> 50 °C). If the heat stimulus is prolonged, stimulation at lower temperatures may occur. Type I receptors become sensitized following tissue damage so that thresholds for stimulation by both heat and mechanical stimuli decrease. Type II Aδ nociceptors have lower heat thresholds and higher mechanical thresholds than type I receptors and are primarily responsible for the first acute pain response to noxious heat. C fiber nociceptors are polymodal, responding to heat, mechanical and chemical stimuli although different sub-populations of C fibers exist. Heat and mechanically sensitive nociceptors are termed CHM's, while another sub-population, termed silent nociceptors, are heat sensitive only in naive animals, becoming sensitive to meachanical stimuli following tissue damage. Silent nociceptors are also more sensitive to chemical stimuli such as histamine than CHM's. Not all C fibers are associated with nociceptors, with some C fibers responding to innocuous stimuli such as cooling. It is important to note that nociceptors are extremely heterogenous, with a variety of different receptors being expressed and neurotransmitters released.

Activation of the nociceptor by different environmental stimuli

1. Heat

Generally A δ and C fiber nociceptors respond to heat at temperatures around 43 ° C, the temperature at which heat stimuli start to cause tissue damage, although type I A δ nociceptors respond at higher temperatures. The most important mechanism by which heat activates nociceptors is through stimulation of receptors of the transient receptor potential (TRP) family, particularly the TRPV1 receptor, although other mechanisms are thought to be involved.

2. Cold

Similar to the detection of heat a number of different receptors are considered to play a role in the detection of noxious cold stimuli and the underlying mechanisms have not been fully elucidated. TRP family receptors such as TRPM8 and TRPA1 are thought to be important as well as some voltage gated Na^+ and K^+ channel receptors.

3. Mechanical

Nociceptors responding to mechanical stimuli can be characterized based on their mechanosensitivity. C fiber nociceptors and slowly adapting A δ mechanoreceptors generally have a high threshold to stimulation by mechanical stimuli, while A δ D hair fibers are activated by light touch. The overall response of the different mechanosensitive fibers allows a full range of stimuli to be detected from touch and vibration, light pressure through to noxious mechanical stimuli. Mechanotransducers are likely to comprise acid sensitive ion channels (ASICS) that detect locally produced protons caused by tissue ischaemia resulting from mechanical stimulation. ASIC1 is known to be important in noxious mechanotransduction, and a role for TRP receptors has also been proposed. Other receptors that are likely important are two pore KCNK potassium channels.

4. Chemical

Transient receptor potential channels, including TRPV1 and TRPM8 and TRPA1 are known to be important in detecting environmental chemicals and endogenous factors produced by physiological stress.

How does activation of the nociceptor by a noxious stimulus result in generation of an action potential in the afferent fiber?

The nervous system encodes and transmits information electrically in the form of action potentials. Activation of the channels described above by different noxious stimuli, if of sufficient magnitude, will cause a depolarization of the receptor membrane, termed a receptor potential. Receptor potentials have the capacity to generate an action potential in the sensory afferent fiber, allowing onward transmission of the signal to the spinal cord. Voltage gated sodium, calcium and potassium channels expressed on C and A δ fibers are recognized to be important in the translation of receptor potentials to generate an action potential, and so are important potential targets for novel analagesics.

Spinal cord

Primary afferent sensory fibers synapse in the grey matter of the dorsal horn of the spinal cord, which is organized into ten anatomical and functionally distinct layers or laminae. Different primary afferent fibers synapse in distinct lamina, depending on whether the sensory fiber is transmitting noxious or non noxious information. The more superficial laminae (I and II) are associated with the processing of noxious stimuli, although laminae I to V all receive sensory input. A δ and C fibers synapse primarily in laminae I and II, although there is also a higher hierarchy of structural and functional organization and different sub-types of C and A δ synapse in different regions of these laminae, for example, peptidergic C fibers (C fibers that release neuropeptides such as substance P) synapse in lamina I and the dorsal part of lamina II, whereas non peptidergic C fibers synapse in lamina II only.

A β fibers that relay primarily non nociceptive input related to mechanosensation and touch synapse in laminae III and IV. Lamina V is unusual compared to others because the primary afferent terminals of sensory fibers conveying both noxious and non-noxious information synapse here. Aβ, Aδ and indirectly C fibers all terminate in this layer. Cells of the dorsal horn can be subdivided into nociceptive specific cells, which predominate in laminae I and II, non-nociceptive (predominantly in laminae III and IV) and wide dynamic range neurons that respond to a range of stimuli from innocuous through to noxious. Wide dynamic range neurons predominate in lamina V. A number of different neurotransmitters are released at the primary afferent terminal, described in more detail under central sensitization. The precise structural organization is likely to facilitate differentiation between noxious stimuli of different intensities and qualities, for example heat or mechanostimulation.

Ascending projection neurons

Projection neurons are predominantly located in laminae I, III and IV and send axons in the white spinal matter to the brain. Primary afferent fibers may synapse directly with projection neurons or via interneurons. Many projection neurons have axons that cross the midline and travel proximally contralaterally. Projection neurons ascend in specific fiber tracts relating to transmission of different types of noxious stimuli, so that the precise structural organization of the dorsal horn of the spinal cord is continued in the white matter.

Axons of projection neurons from laminae I and III target different specific areas of the brain, providing a mechanism by which information relating to nociception can be integrated with information from the autonomic nervous system and the hypothalamic-pituitary axis (HPA). Brain areas that receive direct inputs from the superficial laminae of the dorsal horn include:

1) Caudal ventrolateral medulla, a site of integration of cardiovascular and nociceptive responses, also giving rise to descending projection to the dorsal horn.

2) The solitary tract nucleus (NTS). This brainstem structure also receives multiple inputs from the cardio-respiratory systems and has a role in generating the reflex tachycardia that results from some types of noxious stimulation.

3) The periaqueductal gray (PAG), an important structure for integrating information relating to stressors such as pain and coordinating coping strategies, that may be either active or passive. The PAG plays a key role in the descending control of nociception.

4) The lateral parabrachial area receives input from projection neurons originating in lamina I of the dorsal horn. It is an important relay site, projecting to forebrain structures such as the amygdala and hypothalamus. It is therefore considered to play a role in the emotional, aversive and autonomic components of pain.

5) The thalamus. The ventral posterolateral (VPL) nucleus and the posterior triangular nucleus of the thalamus receive inputs from the dorsal horn of the spinal cord and in turn relay information to the primary and secondary somatosensory cortices and insular cortex.

These pathways are considered to be involved in the both the sensory discriminative (somatosensory cortices) and affective motivational (insular cortex) aspects of pain.

The cerebral cortex

Pain is recognized to be a complex multi-dimensional phenomenon and the cerebral cortex is considered to be the seat of pain perception in mammals. Electrophysiological and functional imaging studies inform us that no one single structure is responsible for the processing of pain, instead the experience of pain is thought to arise from co-activation of a number of different structures within the cerebral cortex.

Two functionally distinct parallel systems are recognized to contribute to pain processing 1) the medial pain system that results in the affective motivational aspects of pain, causing aversion, fear and anxiety; 2) the lateral pain system that leads to the sensory-discriminative aspects of pain, providing information about stimulus location and intensity.

Different brain structures are involved in the two pathways although functional interconnectivity between them ensures that the two systems do not function independently of each other. For example, information about the intensity of pain is likely to determine in part how aversive the experience is likely to be. The anterior cingulate cortex (ACC) and insular cortex are recognized to be key structures in the medial pathway, receiving significant input from medial thalamic nuclei and also contributing to the descending control of pain. In contrast the primary and secondary somatosensory cortices are important structures in the lateral pain pathway, receiving input from the lateral thalamic nuclei.

Pain and the autonomic nervous system

Pain also induces specific changes in the autonomic nervous system. These changes are critical to adaptation and survival and ensure that pain results in appropriate modulation of the cardiovascular and respiratory systems to facilitate a change in behavioural state.

The central autonomic nervous system network is widely distributed throughout the brain, including the ACC and insular cortices, central nucleus of the amygdala, hypothalamus, PAG, parabrachial nucleus of the pons (PBN) and NTS. These brain regions are also intimately involved in the processing of nociceptive stimuli and the perception of pain, such that pain generates stimulus specific patterns of autonomic nervous system activation. Sympathoexcitation, characterized by hypertension and tachycardia, is commonly associated with noxious stimulation in unconscious animals and pain in conscious individuals, but bradycardia and hypotension can also occur. Nociceptive afferents from the superficial laminae of the dorsal horn also project monosynaptically to preganglionic sympathetic neurons in the same spinal segment, forming the basis for segmental somatosympathetic and viscerosymapthetic reflexes.

Cholinergic neurons play an important role in the integration of autonomic and nociceptive systems. There are direct projections from the dorsal horn to catecholaminergic cell groups (A1, C1, A5) in the ventrolateral reticular formation (VLM) and pons. These catecholaminergic neurons project to the hypothalamus, autonomic neurons and dorsal horn, modulating autonomic, endocrine and nociceptive responses. Connections between the PBN and thalamus and amygdala provide a pathway by which nociception and pain trigger emotional and arousal responses associated with autonomic and endocrine activation. The NTS is also an important structure for the modulation of normal homeostatic mechanisms regulating cardiorespiratory activity by some nociceptive afferent fibers. It is thought to be particularly important in the integration of autonomic and sensory visceral information, including nociception.

The PAG is particularly important for integration of the nociceptive and autonomic nervous systems. Cutaneous nociceptive stimuli cause activation of the lateral PAG via the spinal and trigeminal dorsal horn. This initiates flight or fight responses by sympathoexcitation causing tachycardia, hypertension and redistribution of blood to muscles; representing an active coping response to escapable stimuli. The ventral lateral PAG predominantly receives input from muscle, visceral and poorly localized somatic stimuli and initiates responses such as bradycardia and hypotension and hyporeactivity to the environment. These reflect adoption of a passive coping strategy in the presence of inescapable stimuli. Outputs from the lateral and ventral lateral PAG project to different regions of the medulla to allow the appropriate modulation of cardiovascular responses according to stimulus type.

Key differences between the somatic and visceral pain pathways

Visceral pain is common and difficult to manage pharmacologically. The sensation of visceral pain differs markedly from cutaneous pain, reflecting differences in the processing of visceral and cutaneous stimuli. Generally sufferers of visceral pain attribute a greater negative emotional component to it than somatic pain and this is also associated with exaggerated autonomic nervous system responses. Cardinal features of visceral pain are 1) its poorly localized and diffuse nature, 2) it may not be evoked from all internal organs as not all viscera are innervated by sensory afferent fibers, 3) it is not always linked to tissue injury, functional disturbances of the viscera may also result in pain, 4) it is referred to the body wall, 5) it is often accompanied by accentuated motor and autonomic reflexes which are considered to be a reaction to a warning system.

The sensations that can arise from visceral organs are very different than those arising from cutaneous stimuli. Visceral pain results from direct inflammation of a visceral organ, occlusion of bile or urine flow or functional visceral disorders. It is associated with sensations such as distention, bloating, nausea or dyspnoea, a marked contrast to the sensations of heat, touch, pinch and crush that are elicited by cutaneous stimuli.

Central and peripheral sensitization

A unique feature of the pain pathways is that they are not hard-wired. Instead they show marked plasticity; the sensitivity and responsiveness of pain pathways is modulated by the peripheral noxious sensory input into the system. This plasticity is responsible for the changes pain sensation that occur following nerve damage and inflammation. Clinically it is apparent that following tissue injury pain sensitivity is increased, which can make provision of effective analgesia more challenging. Increased sensitivity is thought to serve a protective function, with enhanced pain resulting in greater protection of the damaged tissue. However it can also lead to persistent pain which is maladaptive. The changes in pain sensation that accompany tissue injury are typically **hyperalgesia, allodynia** and **spontaneous pain**. Hyperalgesia is enhanced pain sensation from stimuli that would normally cause pain and can be divided into primary hyperalgesia, which is enhanced sensitivity in the area of tissue damage, and secondary hyperalgesia, which is present in the area of surrounding uninjured tissue. Primary hyperalgesia results in increased sensitivity to both thermal and mechanical stimuli whereas secondary hyperalgesia is generally considered to be to mechanical stimuli only. Allodynia is pain due to a stimulus that does not normally cause pain such as touch. Pain does not normally arise spontaneously without stimulation of the tissue, therefore spontaneous pain is also an aberrant sensation that accompanies central and peripheral sensitization. Sensitization is a feature of both cutaneous and visceral pathways, but the mechanisms of central and peripheral sensitization will be discussed with reference to the cutaneous pathway only.

Peripheral sensitization

Peripheral sensitization, triggered by inflammation, results in peripheral hyperalgesia. When tissue damage occurs it stimulates the release of inflammatory mediators from damaged cells, the endothelial cells of local blood vessels and white blood cells that migrate into the area. Inflammatory mediators include prostaglandin E_2, leukotrienes, cytokines, bradykinin, platelet activating factor, glutamate, nerve growth factor, endothelin and substance P. Collectively these mediators enhance sensory neuron background activity, lower thermal and mechanical thresholds and increase responses to suprathreshold stimuli, all features of peripheral sensitization. Tissue damage also initiates neurogenic inflammation, induced by the efferent actions of sensory nerves. Release of neurotransmitters such as substance P and CGRP by the peripheral terminals of C fibers causes vasodilation and oedema. These neurotransmitters also enhance the release of inflammatory mediators from cells such as mast cells, contributing to sensitization of sensory afferent fibers in a positive feedback loop.

Peripheral sensitization, as well as mediating peripheral hyperalgesia, also contributes to the development and maintenance of central sensitization by increasing C fiber afferent activity into the dorsal horn of the spinal cord.

Central sensitization

Central sensitization, a phenomenon that occurs in the spinal cord, is critical to the development of enhanced pain sensitivity after injury and the development of chronic pain. Understanding key mechanisms that underpin central sensitization is essential for knowledge of pain pathophysiology and analgesic drug action. However these mechanisms are extremely complex and only key points are given here.

Central sensitization is a manifestation of the functional and morphological plasticity in the central nervous system. It comprises both acute and long term changes in nociceptive processing. As a result of central sensitization there is an increase in synaptic strength, change in the receptive field properties of dorsal horn neurons and reduced inhibition of nociceptive processing in the spinal cord, collectively enhancing nociceptive transmission from the peripheral sensory system to the brain and manifesting clinically as increased pain sensitivity.

Under basal conditions glutamate is the most common excitatory neurotransmitter in the dorsal horn of the spinal cord. It is released from the presynaptic membrane of primary afferent sensory fibers and primarily binds to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazelpropionic acid), kainate and G protein coupled metabotropic receptors on the post-synpatic membrane of dorsal horn cells. The NMDA receptor, also present on the post-synaptic membrane does not participate in nociceptive transmission under normal conditions due to blockade by Mg^{2+} ions found in nervous tissue. Although glutamate is the most prevalent excitatory neurotransmitter, other neurotransmitters also play a role, including Substance P and CGRP. Substance P is released by petidergic C fibers and binds to the NK1 (neurokinin) receptor; CGRP, synthesized by small diameter sensory neurons, binds to the CGRP receptor, both found on the post synaptic membrane of dorsal horn cells. Central sensitization is only induced by sustained and intense noxious stimuli that are sufficient to increase C fiber activity and thereby cause prolonged depolarization of the post synaptic membrane of dorsal horn cells. Membrane depolarization removes the magnesium block of the NMDA receptor allowing activation by glutamate and influx of calcium into the dorsal horn cell. This initiates a cascade of events resulting in heightened activity of dorsal horn neurons. Many of these events involve receptor phosphorylation, mediated by protein kinases. Substance P and CGRP also potentiate central sensitization by causing long lasting depolarization of the dorsal horn post synaptic membrane and temporal summation.

Normally only a small percentage of synaptic inputs to dorsal horn neurons contribute to generation of an action potential in the dorsal horn cell. However nociceptive specific neurons in the dorsal horn laminae I and II receive many synaptic inputs from low threshold sensory afferents as well as inputs from nociceptors that lie outside the receptive field of the cell and do not contribute to the output of the cell under normal resting conditions.

Following central sensitization the receptive field of dorsal horn neurons increases so that these subthreshold inputs contribute to cell output and nociceptive specific neurons start to adopt the electrophysiological properties of wide dynamic range neurons. These modifications contribute to allodynia, because Aβ activity (resulting from stimulation of low threshold receptors) becomes interpreted as pain.

This is a brief overview of some of the mechanisms that produce central sensitization. Mechanisms are multiple but all result in increased membrane excitability of dorsal horn cells, increased synaptic efficacy in the nociceptive pathway and reduced inhibition. Consequently nociceptive processing in the spinal cord is facilitated, increasing the barrage of noxious information that is relayed to the brain where it is interpreted as pain.

Descending control of nociception

Descending control of nociception is modulation of nociceptive processing by supraspinal centers and it is an important survival mechanism, allowing implementation of appropriate behavioural responses to life threatening stimuli by decreasing afferent nociceptive input to higher brain centers. However it can also be maladaptive, leading to the development of chronic pain states. Therefore although descending control was previously considered to be inhibitory only, the importance of facilitation of nociceptive processing by supraspinal centers is now accepted. The balance between inhibition and facilitation is dynamic and a switch between a predominance of inhibition to facilitation is likely to underlie chronic inflammatory or neuropathic pain states.

In contrast, acute stress and fear cause hypoalgesia (stress induced analgesia), mediated by an acute increase in descending inhibition of nociceptive processing. The periaqueductal gray – rostral ventromedial medulla (PAG-RVM) system is recognized to be pivotal to descending control, other structures considered to exert a descending influence on nociception are the caudal medulla (dorsal reticular nucleus and caudal lateral ventrolateral medulla) and the pontine noradrenergic cell groups. The superficial dorsal horn is the primary target for descending pathways. The PAG does not connect directly with the superficial dorsal horn, the RVM acts as a relay center between the PAG and spinal cord. The PAG receives multiple inputs from other brain structures, including the hypothalamus and limbic system, acting as a center for integration of nociceptive, autonomic nervous system, cognitive, emotional and behavioural responses.

The descending control of dorsal horn cells is selective for noxious stimuli, activation of dorsal horn cells by innocuous stimuli undergoes limited modulation by descending pathways. Evidence is also is emerging that descending control differentiates between C and A fiber nociceptive input in the deep dorsal horn, such that C fiber input is inhibited to a much greater extent than A fiber input.

The evolutionary advantage of this phenomenon is that A fiber input predominantly provides information on the sensory discriminative aspects of pain, such as intensity and location. Preservation of this information is important for survival, whereas C fiber input is aversive and distracting, suppression allows a more effective behavioural and cognitive response to the threat, increasing chances of survival.

The understanding of descending control pathways and their role in nociceptive processing has significantly increased recently, and the concept that it functions as an inhibitory system only disproven. Modulation of these pathways offers a potential target in the therapeutic management of chronic pain.

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