The Pathophysiology of Pain & Building an Effective Analgesic Protocol for Acute Pain

Following the Pathway for Effective Patient Analgesia

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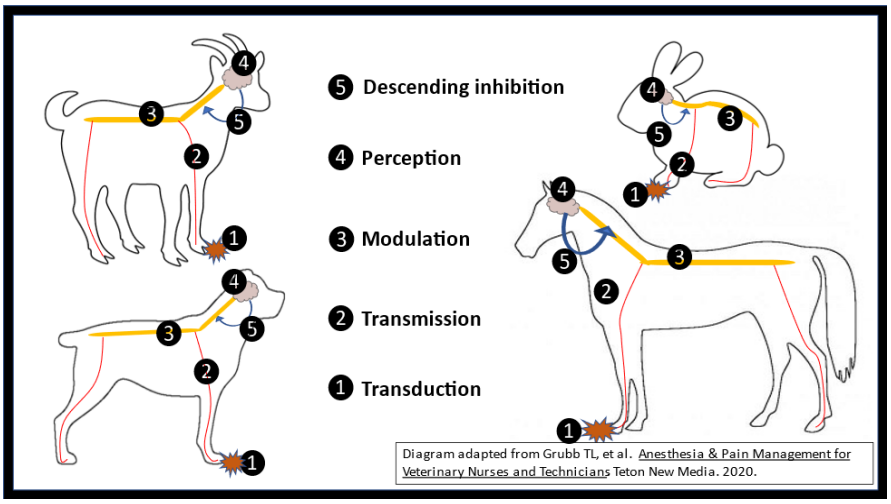
Although there may be individuals who still believe the myth that 'animals don't feel pain', this is actually scientifically impossible. The processes involved in the initiation, propagation and sensation of pain are highly conserved, meaning very similar, across mammalian (and other) species (Broom, 2001, Smith and Lewan, 2009). This means that a stimulus causing pain in a human is scientifically evidenced to cause pain in an animal. Thus, veterinary patients should receive analgesics for the same painful conditions that are treated in humans. Failure to control pain is both an ethical and medical issue, causing a myriad of negative effects on the patient's health, welfare (or 'quality of life') and behavior (Muir and Woolf, 2001, Muir, 2009).

Effective analgesia is best provided using knowledge of the pain process/pathway and administration of drugs/techniques that are most selective for the source or type of pain experienced by the patient. Drugs/techniques with different mechanisms or sites of action in the pain process can be used together to maximize analgesic efficacy. This technique, multimodal analgesia (MMA), is particularly crucial for effective control of moderate to severe pain in humans and in animals (Kazakos & Savvas, 2017, Lamont, 2008; Berry, 2015; Beverly, et al. 2017, Helander et al., 2017). The following is a brief overview of the pain process as related to effective pain management. More in-depth reviews are available (Muir and Anderson, 2005 [cattle], Muir, 2010 [horses], Fox, 2010, Shilo and Pascoe, 2014, Bell, 2018, Self and Grubb, 2019).

Understanding the Pain Process/Pathway and Maximizing Analgesic Efficacy

Pain is defined by the International Association for the Study of Pain (IASP; 2017) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. This rather awkward-sounding definition is actually useful because it describes the value of pain in protection from injury. A paw placed on a sharp rock causes activation of the pain pathway, the paw is reflexively withdrawn and tissue damage is prevented, or at least reduced. Thus, pain can be a normal physiologic response which is called 'physiologic' or 'protective' pain. Pain can also be an abnormal response causing a state of intense and/or prolonged pain that is not protective from tissue damage, which is called 'pathologic' or 'maladaptive' pain (Fox, 2010, Shilo and Pascoe, 2014, Adrian et al., 2017, Bell, 2018, Self and Grubb, 2019). Pathologic pain can occur due to a variety of reasons, including severe tissue trauma, prolonged inflammation, direct damage to the nervous system (eg, nerve root tumors, herniated intervertebral disc, etc…), and untreated or under-treated pain, especially if the pain is moderate to severe.



The Pain Pathway

The initiation, propagation and sensation of pain is a very dynamic and complex event that involves integration of a variety of physiologic processes, receptors, neurotransmitters, neural fibers, neural pathways and both discrete and diffuse anatomic locations from the periphery to the central nervous system (CNS). These components are dynamic or 'plastic' and often change their structure, function or activity according to the pain source, intensity and/or duration. Although they are not discrete entities, the components of the pain process can be loosely divided into a series of continuous and overlapping 'steps' that is called the 'pain pathway'. The steps include transmission, transduction, modulation and perception. Because of its role in analgesia, descending inhibition, which is technically a component of modulation, is listed as a separate step in this discussion.

Transduction: The prefix 'noci' means 'injury' or 'pain' and the pain pathway is initiated when a specialized, peripheral sensory receptor, or 'nociceptor', is depolarized by a noxious, or 'nociceptive', stimulus. Depolarization of the nociceptors *transduces* the mechanical information from the stimulus into an electrical impulse. The density and exact distribution of nociceptors may vary by species and can be impacted by age and disease but are commonly highly represented in the skin and located throughout most structures in the body including the muscles, tendons, bone, viscera, peritoneum, pleura, periosteum, meninges, joint capsules, blood vessels, etc…. (Woolf and Ma, 2007; Smith and Lewan, 2009)

The nociceptors are not traditional 'receptors' but are the free endings of A-delta and C nerve fibers that will transmit the stimulus to the CNS (Woolf & Ma, 2007). Most of the nociceptors, especially those from C fibers, are 'polymodal', meaning that they can be depolarized by a variety of noxious stimuli from mechanical, thermal and chemical sources. Thus, as examples, noxious stimuli from surgery, trauma, burns and skin contact with acids are all recognized as pain. In physiologic pain, the nociceptors require a noxious stimulus to depolarize, there is no spontaneous nociceptor depolarization. In addition, the nociceptors are high threshold, meaning that they respond only to noxious stimuli and not non-noxious stimuli like touch (Woolf & Ma, 2007). With tissue injury, damage from structural and inflammatory cells (eg, neutrophils, mast cells, macrophages, and lymphocytes) causes a release of intracellular compounds and recruitment of other compounds (eg, H+, K+, histamine, prostaglandins, etc…) that accumulate in the area of the injury, potentially damaging adjacent cells, and thus expanding the area of cellular damage and inflammation. If the original insult causes minimal tissue damage and inflammation and/or if analgesic treatment specific for this inflammatory process is administered, the expanding tissue

damage can be minimized, and pain maintained as physiologic. However, if the tissue injury is moderate to severe and/or inadequate analgesia is administered, the area of inflammation may continue to enlarge. Within the area of inflammation more nociceptors depolarize, nociceptor threshold is reduced so non-noxious stimuli can cause them to depolarize, and some may depolarize spontaneously. This expanded and exaggerated pain response is 'pathologic pain', or pain in excess of that needed for protection, and the process just described is termed *peripheral sensitization.* Peripheral sensitization increases the number of pain signals that are sent to the CNS, thereby increasing the level of pain experienced by the patient. Peripheral sensitization is a major component of hyperalgesia, which is moderate to severe pain elicited by what should be a mildly painful stimulus. The clinical impact of hyperalgesia is the need for more aggressive analgesia for the patient, even if the patient is admitted for something considered to be low-level pain. For instance, a dog or cat with osteoarthritis is expected to be more painful after a minor surgery than a dog or cat with no preexisting pain.

Prevention or suppression of the pathologic pain response at transduction is an integral component of effective analgesia. Because the physiologic pain process (and the pathologic process at least in part) at transduction is primarily driven by inflammation, the most effective currently-available drug class at this pain pathway step is the anti-inflammatory drug (NSAID) class. When inflammation is predicted, the timing of anti-inflammatory drugs is important as NSAIDs are generally more effective when administered preoperatively versus postoperatively (example: Lascelles et al., 1998). NSAIDs are more effective when combined with drugs that work in other parts of the pain pathway like opioids (example: Mwangi et al., 2018)

A novel drug class, the anti-nerve growth factor monoclonal antibody (anti-NGF mAb) class, has also shown to be very effective at transduction, at least for the treatment of chronic pain (Enomoto et al., 2019). Local anesthetics, the application of ice (cryotherapy), acupuncture, photobiomodulation (ie, laser therapy) and capsaicin are examples of other drugs/treatments that have some degree of efficacy at transduction.

Transmission: In the transmission step of the pathway, each depolarized nociceptor *transmits* a stimulus, or action potential, from the A-delta and C fibers to the CNS, primarily through opening of sodium channels (Levinson et al., 2012). In pathologic pain, additional A-delta and C fibers can be recruited, A-beta fibers (which normally transmit touch) can be altered to transmit noxious stimuli, and some Na+ channels can become hyperexcitable and exhibit spontaneous electrical activity (Levinson et al., 2012). These processes increase the number and frequency of nociceptive impulses transmitted to the CNS, thus amplifying the pain signal.

The local anesthetic drugs, which block sodium channels, are an integral part of pain control at transmission. This is a unique and powerful mechanism in the pain pathway and local/regional blockade is recommended for all patients, if possible (Mathews et al., 2014, Grubb & Lobprise 2020). As with NSAIDs, administration of local anesthetics prior, to versus after, the initiation of pain is generally more effective (example: Savvas et al., 2008) and inclusion of local blocks with other analgesic drugs improves analgesic efficacy (examples: Ko et al., 2009, Warrit et al., 2019).

Examples of other analgesic drugs/treatments with some efficacy at transmission include opioids and alpha-2 agonists combined with local anesthetics, cryotherapy, acupuncture, and anti-NGF mAbs.

> NOTE: Transmission as an ascending *analgesic* pathway: A-beta receptors and fibers, which are located with the A-delta and C fibers, generally conduct non-noxious (non-nociceptive) stimuli such as touch and movement. Stimulation of the A-beta fibers can also recruit inhibitory neurons in the dorsal horn of the spinal cord. This appears to be a component of the

explanation of why gently rubbing a painful site may temporarily decrease the level of pain ('gate control'; Melzak and Wall, 1965).

Modulation: This step of the pathway, which occurs at the dorsal horn of the spinal cord, is very complex, with numerous possible scenarios, including changing or '*modulation*' of the intensity of the pain stimulus (D'Mello and Dickenson, 2008). The A-delta and C fibers terminate in various lamina in the dorsal horn of the spinal cord where neurotransmitters (primarily glutamate and substance P) are released. In the simplest form of physiologic pain, the impulses are sent to the contralateral side of the spinal cord and then transmitted directly to the brain via ascending (or 'projecting') tracts without modulation.

Modulation is often excitatory (numerous processes) but, as just previously described, can be inhibitory (eg, ascending A-beta fiber input or input from the descending inhibition). Inhibitory input can be a component of physiologic pain or activated in an endogenous attempt to control pathologic pain. In pathologic pain, excitatory modulation is often pronounced because the pain signal can be amplified by processes that are numerous, complex and dynamic. The initiation of excitatory modulation is often driven by peripheral sensitization but can also be due to direct nervous system injury. Increased excitatory activity in the spinal cord, or *central sensitization* or *central plasticity*, means an increased number of pain stimuli sent to the brain, and greater pain for the patient. This can cause hyperalgesia and/or allodynia, which is a pain response to a nonpainful stimulus. This is often seen as an exaggerated behavioral response, like a rapid withdrawal from, or aggressive move towards, the perceived source of the stimulus. The clinical impact is the critical need for multimodal analgesia, potentially aggressive multimodal analgesia, since central sensitization is multifaceted and results in extreme pain.

A major contribution to central sensitization is activation of N-methyl-D-aspartate (NMDA) receptors, which are normally dormant. This leads to numerous avenues of pain amplification, including recruitment of additional pain receptors, lowered threshold of pain receptors and downregulation of opioid receptors (ie, 'opioid resistance'). Ketamine, administered as a sub-anesthetic infusion (but potentially also delivered by other routes), is an important therapeutic choice because it prevents/reverses central sensitization by 'plugging' the NMDA-receptors. Although research in ketamine infusion-mediated analgesia is in its infancy in veterinary medicine, evidence from human medicine supports the use of ketamine in both acute and chronic pain (Cohen et al., 2018, Schwenk et al., 2018).

Examples of other drugs/treatments that have some efficacy at modulation include opioids, alpha-2 agonists, systemic lidocaine, neurokinin-1 receptor antagonists, etc… Drugs/treatments that work in the transduction and transmission phase of the pathway have an impact on modulation by decreasing the number of pain signals that reach the dorsal horn of the spinal cord.

Perception: The perception of pain by the patient is also a very complex process mediated by the number of pain signals reaching the brain and impacted by a variety of other factors, like age, health status, level of stress/fear and previous pain experience. Perception is not completely understood in humans, who can communicate what they are perceiving, and is even less-understood in animals, who generally don't communicate in a way that humans understand. It is known that there is no specific pain center in the brain, and nociceptive impulses from the spinal cord arrive at a variety of anatomical sites (eg, the thalamus, hypothalamus) where they synapse and transmit signals to various cortical and subcortical regions (eg, the somatosensory cortex, periaqueductal gray region (PAG)). This diverse pattern of distribution results in a variety of outcomes, which includes pain perception along with

arousal/wakefulness (which contributes to insomnia in painful patients), behavior changes and emotional responses.

Many of the drugs/treatments that work in the spinal cord also work in the brain, including the opioids, alpha-2 agonists, NMDA-receptor antagonists, tricyclic antidepressants, norepinephrine and serotonin (5-HT) reuptake inhibitors, etc.

> *Definition clarification and role of inhalant anesthetics:* An understanding of 'nociception,' versus 'pain' is based on what happens, or doesn't happen, in the brain. *Nociception* describes strictly the neural process that occurs beginning with transduction of a painful stimulus but without ending in a cognitive processing of that stimulus. This definition is often used for phyla (eg, invertebrates) that don't seem to have a central processing center (although this may be incorrect). *Pain* is defined as a cognitive or emotional response to nociception that occurs in the higher centers of the CNS, such as the cerebral cortex. Thus, our patients experience pain. However, inhalant anesthetics block perception, thus pain technically doesn't occur in anesthetized patients since the cognitive or emotional response would be prevented by the anesthetic. However, with noxious stimulation, the other components of the pain pathway are activated, causing adverse effects from the noxious stimulus during anesthesia (eg, tachycardia, neuroendocrine responses, etc…). The patient will experience pain, along with the adverse effects of pain, on emergence from anesthesia if pain is un- or under-treated during anesthesia.

Descending inhibition: Descending inhibition of pain impulses can be activated in various central sites and its main effective site is the dorsal horn of the spinal cord through release of inhibitory neurotransmitters (eg, endogenous opioids [endorphins, enkephalins, dynorphins], serotonin, etc…). The major importance of descending inhibition is that decreased efficacy of descending inhibition may play a large role in pathologic pain, central sensitization and allodynia (Ren and Ruda, 2002). Exogenous stimulation of descending inhibition has only minor contributions to pain control in physiologic pain but could potentially play a larger role in pathologic pain. Drugs/treatments with some efficacy at descending inhibition include exogenously administered opioids, treatments that cause the release of endogenous opioids (eg, acupuncture), serotonin and norepinephrine reuptake inhibitors (Moore, 2016) and drugs that increase the inhibitory neurotransmitter gamma aminobutyric acid (GABA).

Conclusion

Perhaps the myth that animals don't feel pain stems from the fact that animals don't convey pain in ways that humans readily recognize. This is eloquently described by the IASP (2017), 'inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain'. With a basic understanding of the pain pathway, 1) the fact that animals do feel pain can be scientifically supported and 2) effective analgesic protocols based on the site/mechanism of action of the drug/treatment can be developed.

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