Pain Pathway

Lysa Pam Posner DVM, DACVAA
College of Veterinary Medicine
North Carolina State University

Pain is one of the most common symptoms patients are presented for veterinary care (lameness, abdominal discomfort, traumatic injury, etc). Aside from the humane need to relieve suffering, pain itself causes a host of physiologic consequences that can contribute to morbidity and mortality. Treating pain can be challenging and frustrating. Understanding how pain information is processed and attenuated (lessened) can help the veterinary professional to design successful analgesic therapies for their patients.

Definition of Pain from IASP (International Association for the Study of Pain)[1]

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

"The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment."

Pain is often discussed in 2 categories:
1. Physiologic Pain ("warning pain") which occurs after noxious stimuli (brief perception). It is generally sharp and is protective as it occurs before actual tissue damage occurs.
2. Pathologic Pain ("clinical pain") which occurs in response to tissue damage. It is generally a dull burning pain that is often accompanied by hyperalgesia and allodynia.

Review of Pain Pathways

Fibers of primary sensory neurons
Aβ fibers are large, myelinated nerves with a low threshold for activation. They generally transmit pressure and innocuous sensations, but can be recruited to transmit noxious stimuli with pathology.
Aδ fibers are small, myelinated nerves, with a high threshold for activation. They also transmit cold sensory input. Information from these fibers is considered the "first" pain which is sharp, well localized, and stops soon after stimulation.
C fibers are small, unmyelinated nerves with a high threshold for activation. They transmit heat and cold information, and inflammatory pain (silent receptors). Information from these receptors are considered the "second" or "slow" pain, which is described as burning, or diffuse, and continues after initiating stimulus.

Nociceptors are free (naked) nerve endings. They transduce energy into electrical impulses (encode mechanical, chemical, thermal energy). Nociceptors generally have a high threshold for activation and signal actual or potential tissue injury. Nociception is the detection of noxious stimulus (that in humans results in "pain").

<u>Types of Nociceptors</u>
1. Mechanoreceptors (respond to pressure and pinprick)
2. Poly-modal mechano-heat receptors (respond to excessive pressure, extreme temperature, or allogens (pain producing substance))

3. Silent nociceptors (inflammation) are subtype of C-fibers (recruited in the face of inflammation).

4 Components of Pain Transmission
1. Transduction (noxious stimuli to neural pathway)
2. Transmission (rostral movement in pathway)
3. Modulation (of signal (+/-))
4. Perception (conscious perception = pain)

1. Transduction
In short, transduction is the transformation of a noxious (painful) stimulus into an action potential which can then be transmitted via a sensory nerve. Nociceptors (pain sensing receptors) or 1st order neurons are naked nerve endings in periphery with cell bodies in dorsal horn ganglia. They encode mechanical, chemical, thermal or electrical stimulus that is "transduced" to afferent action potentials on nerves (Aδ or C fibers nerves). The action potentials are propagated by Na^+ channels. 1st order neurons synapse with neurons in dorsal horn of the spinal cord (2nd order neurons).

2. Transmission
Transmission is the rostral or ascending movement of action potentials (via Na^+ channels) within pain pathway. Transmission of action potential occurs via either peripherally nerves or ascending spinal tracts within the spinal cord. The spinothalamic tract (STT) is most prominent nociceptive pathway although many alternative routes are present. The transmission of 2nd order neurons terminates in the thalamus. The final destination for pain information is the cerebral cortex.

3. Modulation
Sensory information can undergo either inhibition or enhancement. Inhibition or enhancement can occur peripherally, at the dorsal horn of the spinal cord or in the brain. Peripherally, enhancement of the signal, for example, could be from inflammatory cytokines at site of injury, whereas inhibition could be from the administration of NSAID drugs. The dorsal horn of the spinal cord is often called the "gate" as it is responsible for attenuating and enhancing information (more about gating of information later). Many analgesic drugs work to attenuate the pain signal at the dorsal horn (opioids, alpha-2 agonists, NMDA receptor antagonists). The brain also is a site of modulation, as a site of action for both endogenous (e.g. endorphins) and exogenous drug binding (opioids, alpha-2 agonists, NMDA receptor antagonists).

4. Perception
The conscious perception of a noxious stimulus is generally considered pain. 3rd order neurons transmit information from the thalamus to higher (cortical) brain centers. If a patient is anesthetized with a general anesthetic and the skin is cut, the entire pain pathway is activated up to the cerebral cortex (which is asleep). Without the conscious perception the patient does not "feel" pain. However, if the general anesthetic removed (turned off); the brain is now awake while the entire pain pathway is activated. It is therefore important to separate anesthesia from analgesia when designing analgesic protocols.
Where are the nociceptors?
Aδ and C fibers have wide and variable distribution and density.
1. Superficial somatic: skin, SubQ, mucous membranes
2. Deep somatic: muscles, tendons, joint capsules, periosteum, subchondral bone, fascia
3. Visceral: peritoneum, pleura, internal organs, blood vessels. Visceral nociceptors are mostly silent nociceptors and are minimally affected by cutting, burning, crushing. However, they are activated by spasm, stretching, ischemia, and inflammation. Visceral pain can be hard to localize and may expressed as referred pain.

Visceral Nociception is different from somatic nociception as life threatening disease not always painful (i.e. perforation). Visceral nociception is associated with sympathetic ganglia which when activated can cause nausea and malaise. This explains why horses with visceral pain generally sweat more than horses with orthopedic pain.

Peripheral Sensitization occurs when damaged cells produce chemical mediators. These molecules act synergistically creating a "sensitizing soup" which promote vasodilation; increased permeability, and recruits inflammatory cells. This lowers the threshold for Aδ and C fiber activation and causes recruitment of "silent nociceptors" (c-fiber) that respond to inflammation. Antiinflammatory drugs can attenuate the response (e.g. NSAIDs).

Central Sensitization / Wind-up occurs due to changes in dorsal horn neuron excitability. There is an activity dependent long lasting depolarization such that there is a summation of potentials: therefore seconds of C-fiber activation can generate minutes/ hours of post-synaptic depolarization ("wind-up). Central sensitization results in a decreased activation threshold, and increase responsiveness and recruitment of novel inputs (Aβ fibers). There is often a zone of secondary hyperalgesia (increased sensitivity in neighboring areas) and allodynia (responsiveness to stimuli not normally noxious). Wind-up is mediated by NMDA receptors (bind glutamate), tachykinin receptors (bind SubP and neurokinin A). Ketamine is an antagonist at NMDA receptor and can interrupt or prevent wind-up. In preventing/treating wind-up, ketamine is effective at sub-anesthetic doses.
Dorsal horn "gating" modulates what information is passed through the dorsal horn. It is self modulation (inhibitory and enhancing). Providing other stimulation to the dorsal horn can affect which information is let through. Consider the stimulating Aβ fibers (normally not painful). By rubbing a painful area, it is possible to attenuate a pain perception.

Acute pain facilitates tissue repair. The hypersensitization of affected area and surrounding tissue decreases amount to external stimulus allows for healing to occur uninterrupted. The pain response is proportional to the injury and generally responds well to most analgesics.

Chronic pain is pain that persists beyond expected time frame > 3-6 months (humans)
There is autonomous or sustained noxious insult (inflammation) e.g. cancer, osteoarthritis, phantom limb pain. Chronic pain serves no biologic/ protective function. The neuroendocrine response attenuated and there is poor response to conventional analgesics. However, local anesthetics (e.g. lidocaine) and anticonvulsants (gabapentin) decrease spontaneous firing from traumatized or sensitized neurons and are generally more successful.

Neuropathic Pain is produced as a result of nerve damage (compression, transection, inflammation, chemical, radiation, surgery, tumor). There is an altered sensory processing of stimuli or ectopic activity (discharge) from axons, neuroma, or cell bodies. Pain is described as burning. There can be a loss of sensitivity, allodynia, and hyperresponsiveness. Neuropathic pain is mediated by NMDA receptor windup. Drugs that decrease spontaneous firing (local anesthetics and anticonvulsants) may also be useful.

Referred Pain is usually associated with visceral pain. It occurs either via "convergence" since both visceral and somatic input converges in Lamina V or by "facilitation" in that more sensory information normally comes from somatic nociceptors and the brain "assumes" the signal is somatic.

Neural circuitry and species
There is evidence that primates, mammals, birds, amphibians, reptiles and fish have the circuitry to "feel pain". There is also evidence that the perception, distribution of nociceptors, and response to nociception differs within and between species.

Neonatal Hypersensitivity
Neural circuitry is intact at birth.[2] Mechanoreceptors have collateral neurons that extend throughout dorsal horn (vs specific lamina).[2] Therefore it is likely that neonates have exaggerated pain perception. The behavioral response to pain is different in neonates than in adults. There is also evidence there is plasticity of the neonatal CNS and significant pain during this developmental time can alter pain perception for a lifetime.

Preemptive Analgesia has been shown to attenuate central sensitization. For prevention of central sensitization, analgesic must be given before or very soon after pain. Human patients with pre-op and post-op analgesia had lower pain scores and a smaller production of cytokines than those just receiving post-op analgesia. Preemptive analgesia also helps prevent/ attenuate neuropathic and chronic pain states

Physiologic Response to Pain

Animals in pain have varied physiologic responses. There is overall a generalized increase sympathetic tone (↑ NE).

1. Cardiovascular Effects: The increase in sympathetic tone cause an increase in cardiac output (CO), stroke volume (SV), heart rate (HR), and systemic vascular resistance (SVR). This results in increased myocardial work, myocardial O2 consumption, and myocardial irritability.
2. Respiratory Effects: Increased sympathetic tone causes in increase in total body O_2 consumption and CO_2 production. To compensate, there is an increased minute volume (either by increasing tidal volume or respiratory rate). Patients with thoracic or abdominal pain may not keep up with increased respiratory demands due to guarding/splinting. Decreased movement of the check can decrease functional residual capacity and further decrease pulmonary function.
3. GI/GU Effects: Pain results in decreased intestinal and urinary motility; which can lead to ileus (colic) and urinary retention. There is also an increase in HCl production which can lead to ulcers/inappetence.
4. Endocrine Effects: The hormonal response to stress increases catabolic hormones (catecholamines, cortisol, and glucagon) and decreased anabolic hormones (insulin and testosterone). Increased sympathetic tone increases the catabolism of fat and protein which can lead to decreased healing and negative nitrogen balance. Increased sympathetic tone also causes renal retention of Na^+ and H_20 which causes a secondary expansion of the extracellular space.
5. Hematologic Effects: Pain/stress increases platelet adhesiveness and reduces fibrinolysis which can result in hypercoagulability.
6. Immune Effects: Pain/stress produces a leukocytosis with lymphopenia. Depression of the reticuloendothelial system can lead to infection.
7. (Human) Sense of Well-being: Most humans respond to pain with anxiety and sleep loss. Prolonged pain is associated with depression and/or anger.
8. Outcome: Animals in pain have a greater morbidity and mortality. Animals in pain have longer hospitalization, more complications, and die more often. Horses with better analgesia after colic surgery, loss less weight, has less pain associated behaviors and left the hospital earlier![3]

Recognition of Pain in Animals

Recognition of pain in animals is one of the most important and difficult things a veterinarian does. Identification of pain should involve evaluating some if not all of the following parameters; temperament/ interaction, posture, physiologic parameters, and endocrine/chemical markers. It should also be noted that horses are prey animals at to that end have no evolutionary advantage to show pain and thus their signs are often more subtle.

Pain scoring

Subjective Schemes: Many assessments of pain are made based on the observers "gut-feeling" and experience about what an animal in pain looks like. There are HUGE differences from species to species and animals to animals how or if they express pain. In general, prey animals are quite good at hiding pain (there is no evolutionary advantage to showing you are ill if you are prey).

Visual Analog Scale (VAS): is a subjective assessment where the assessor (or the patient) makes a mark on a line with the left-most end being no pain at all and the right-most end being the worst pain possible. After the assessor marks on the line…the line is measured and a number is generated for scoring purposes.

Multi-factorial schemes (e.g. Glasgow Pain Score) use a combination of physiologic and behavior signs to create a number score for pain assessment. Pain scores should be particular to species as posture and attitudes are different between species (compare a horse in pain to a dog in pain). Although these pain scores have shown to be associated with pain/pain states, there are ALWAYS animals for which the pain scale fails!

The British Veterinary Association Animal Welfare Foundation is funding work to assess facial (grimace response) in horses. Facial distortion has proven well correlated in humans and mice.