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Review

Pathophysiologic mechanisms of pain in animals – A review

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The sense of pain is of practical significance in human and veterinary medicine. Its management and prevention constitute integral and fundamental parts of quality and compassionate care of patients. In order to recognise, assess, prevent and treat pain, an understanding of its pathway and the pathophysiologic mechanisms is necessary. This review discusses definitions of pain, its classification, description, pathophysiologic mechanisms, neuro-transmission and evaluation of pain as well as physiological responses to pain, with special reference to domestic animals. It is concluded that adequate understanding of pathophysiologic mechanisms of pain and the physiologic responses of animals to pain may aid its efficient management.

Key words: Pain, definitions, pathophysiologic mechanism, animals, review.

INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey, 1979). Molony and Kent (1997) described pain as an aversive sensory and emotional experience, representing awareness by the animal of damage or threat to tissue integrity. Broom and Fraser (2007) described it as an aversive sensation and feeling, associated with actual or potential tissue damage. Pain is derived from the Latin word `Poena` which means 'punishment'. The understanding of pain is very important and it is viewed from four points based on its pathophysiology: nociception, pain, suffering and pain behaviour (Woolf, 2004).

All tissue injuries, including that from elective surgery, may cause pain. Pain-induced stress responses mediated by the endocrine system, are one of the negative consequences of pain. Increased cortisol, catecholamines and inflammatory mediators cause tachycardia, vasoconstriction, decreased gastro-intestinal motility, delayed healing and sleep deprivation. In addition, trauma causes unseen changes in the central nervous system (CNS). Inadequate pain prevention or management leads to magnification of pain perception and a prolongment of pain state (Heller et al., 2007). If pain is left untreated or

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under-treated, animals become depressed, lethargic, withdrawn, and eventually immobile (Gleed and Ludders, 2008).

Pain medicine can be daunting and challenging, the ability to offer a safe and effective therapeutic regimen is very important, especially in the setting of the opioid abuse epidemic (Smith and Pappagallo, 2013). A broad knowledge of the pathophysiologic mechanism of pain, its pharmacology and pharmacokinetics, may aid in the use of medications and injections for clinical pain therapy.

WHY TREAT PAIN?

Pain control for routine management procedures is considered one of the most important welfare priorities in livestock production today. This is particularly true at a time when public scrutiny regarding animal production and care is high (Bayvel, 2004). Although there is a plethora of published scientific studies dedicated to assessing pain as well as strategies aimed at reducing it, the current knowledge of food animal pain, its assessment and alleviation are still very limited (Flecknell, 2000). Current positive attitudes about animal welfare have increased the importance of pain management in livestock. Even minor surgical procedures in livestock are now performed using a combination of regional, local or general anaesthesia combined with uninterrupted post-surgical analgesia. Attitudinal changes based on current knowledge and enlightenment toward animal suffering have necessitated the understanding of pain modulation by large animal veterinarians and the willingness of clients to incur extra cost for the alleviation of pain in their animals (Bayvel, 2004).

Pain is a percept consisting of initial nociception, followed by a slower but integrated emotional phase. The cerebral cortex, thalamus and the limbic system are involved in pain processing, so specific behaviours to painful stimuli depend upon species, breed, temperament and rearing (Kamerling, 1993).

CLASSIFICATION OF PAIN

Although traditionally, pain can be categorized as acute or chronic based on duration. A more contemporary approach considers pain as adaptive or maladaptive (Woolf, 2004). Adaptive pain is a normal response to tissue damage. Adaptive pain includes inflammatory pain which is a major component of many pain states. Woolf (2004) opined that acute pain disappears once the damaged tissue has been healed. In contrast, chronic (or persistent) pain lasts beyond the expected healing time for an injured tissue (Molony and Kent, 1997). Chronic pain can be more difficult to recognise because it is not possible to identify behaviour that would uniquely and reliably indicate its existence (Mogil and Crager, 2004). It is also important to realise that various tissues and organs of the body can have different sensitivities to painful stimulation. For example, mucous membranes, cornea or dental pulp are considered to be extremely sensitive, whereas parenchymatous organs are less painful (Henke and Erhardt, 2001).

Physiologically, pain is divided into two categories/classes: nociceptive and neuropathic (IASP, 2012). Nociceptive pain is the perception of painful sensation and it is generated by an injury that activates nociceptors in peripheral tissues (Loeser and Treede, 2008). Reports suggest that the nociceptive system may be altered in chronic inflammatory pain (Woolf, 2004). Neuropathic pain is the pathology of the somatosensory system, either in its peripheral elements (peripheral neuropathic pain) or in the CNS (central neuropathic pain) (Loeser and Treede, 2008). It is either central or peripheral (outer surface), depending on the origin of the stimulus; for example, direct damage to the spinal cord or the peripheral nerves, respectively (Carroll, 2009).

Nociceptive pain

Nociceptive pain is further divided into two categories: somatic and visceral. Somatic body pain, which in humans has been described as localized, sharp, aching, or throbbing pain, originates from skin and connective tissues, including the muscles, joints and bones (Faries, 2010).

Somatic pain originating in the skin is called superficial pain. If it originates in the connective tissues such as the muscles, bones and joints, it is called deep pain. In other words, somatic pain refers to pain originating from the periphery and can be, in most cases, well localised (Robertson, 2002).

Visceral (organ) pain is usually dull or hard to localize and originates from receptors in the heart, lungs, kidneys, liver, gastro-intestinal tract, uterus or bladder. Painful states are caused particularly by tissue or nerve damage, inflammatory processes, viral infections or demyelination and are characterised by pain hypersensitivity (Vinuela-Fernandez et al., 2007). Visceral pain arises from the viscera (Joshi and Gebhart, 2000). McMahon et al. (1995) suggested that the sensitivity of viscera to mechanical, thermal or chemical stimuli is very different. Information from certain regions of viscera converges on spinal neurones and pathways that also convey information from somatic structures. For example, some cows exhibit an extreme sensitivity in the region of the sternum, when they suffer from traumatic peritonitis caused by a wire or nail perforating the wall of the fore- stomachs (Frandson et al., 2009).

Nociceptive pain can be acute (short-lived, remitting) or persistent (long-lived, chronic) and may primarily involve injury to somatic or visceral tissues. Pain that is inferred to be related to on-going activation of nociceptors that innervate somatic structures, such as bone, joint, muscle and connective tissues, is termed as “somatic pain”. This pain is recognized by identification of a lesion and characteristics that typically include a well-localized site and an experience described as aching, squeezing, stabbing or throbbing (AMA, 2010). Arthritis and metastatic bone pain are the examples of somatic pain (Landa, 2012).

Pain arising from stimulation of afferent receptors in the viscera is referred to as visceral pain. Visceral pain caused by obstruction of hollow viscous is poorly localized and is often described as cramping and gnawing, with a daily pattern of varying intensity; however when organ capsules or other structures such as myocardium are involved, the pain usually is well localized and described as sharp, stabbing or throbbing, descriptors similar to those associated with somatic pain (AMA, 2010). Visceral pain is usually described as more diffuse and unpleasant than somatic pain (Paine et al., 2009) and the diffuse nature of true visceral pain is probably due to the low density of visceral sensory innervations and extensive divergence of the visceral input within the CNS (Giamberardino and Vecchiet, 1997).

Neuropathic pain

Neuropathic pain originates within the nervous system itself and arises as a disorder of processing of nociceptive activity or as a result of abnormal activity in nociceptive pathways (Lamont et al., 2000). Neuropathic pain is typically manifested by disproportionate hypersensitivity to stimuli (hyperalgesia), abnormal pin and needle sensations (hyperpathia) and nociceptive responses to harmless stimuli (allodynia) (Leung and Cahill, 2010).

Idiopathic pain

It is necessary that patients who have acute or persistent pain without a known physical source should not be inappropriately labeled. This may lead to inadequate assessment in the future and therapeutic decisions that are inappropriately skewed; unfortunately, in many quarters, it also leads to stigmatization of the patient and the potential for greater suffering on this basis. When reasonable inferences about the sustaining pathophysiology of a pain syndrome cannot be made, and there is no positive evidence that the aetiology is psychiatric, it is best to label the pain as “idiopathic” (AMA, 2010).

PATHOPHYSIOLOGIC MECHANISMS OF PAIN

Neurones have evolved specialized properties that allow them to receive information, process it and transmit it to other cells. The stimuli translated into nerve impulses include, light, pressure, chemicals, temperature, vibration and sound waves. Sensory reception begins in receptor cells, specialized to respond to particular kinds of stimuli and transmitted through a corresponding nerve fibre (afferent neurones) to the CNS for processing (Stillwell, 2009). Enormous strides have been made in understanding the neurophysiology and neurochemistry of the systems that transmit and modulate information about noxious events (Willis, 2007). Much also is known about acute inflammation which commonly drives these neural processes. In contrast, relatively little is known about the pathophysiology underlying most persistent pain syndromes (AMA, 2010). Nonetheless, it is now widely accepted that persistent pain may be sustained by different types of mechanisms and clinical characteristics can be used to broadly divide pain syndromes into nociceptive, neuropathic, psychogenic, mixed or idiopathic (AMA, 2010).

Two major classes of nociceptors exist (Meyer et al., 2008). The first includes medium diameter myelinated (Aδ) afferents that mediate acute, well-localized “‘first”’ or fast pain while the second class of nociceptor includes small diameter unmyelinated “C” fibers that convey poorly localised “second” or slow pain (Basbaum et al., 2009). Primary afferent nerve fibers project to the dorsal horn of the spinal cord, which is organized into anatomically and electro-physiologically distinct laminae (Basbaum and Jessell, 2000); by contrast C nociceptors project more superficially to laminae I and II. The stratification of afferent subtypes within the superficial dorsal horn is further highlighted by the distinct projection patterns and circuits engaged by C nociceptors (Braz et al., 2005). The most ventral part of lamina II is characterized by the presence of excitatory interneurons that express the gamma isoform of protein kinase C (PKC), which has been observed in injury-induced persistent pain (Malmberg et al., 1997).

Neumann et al. (2008) indicated that this PKCγ layer is targeted predominantly by myelinated non-nociceptive afferents. Projection neurons within laminae I and V constitute the major output from the dorsal horn to the brain (Basbaum and Jessell, 2000). These neurons are at the origin of multiple ascending pathways, including the spinothalamic and spinoreticulothalamic tracts, which carry pain messages to the thalamus and brainstem, respectively. Attention has now been focused on spinal cord projections to the parabrachial region of the dorsolateral pons, because the output of this region provides for a very rapid connection with the amygdala, a region generally considered to process information relevant

to the aversive properties of the pain experience (Basbaum et al., 2009). From these brainstem and thalamic loci, information reaches cortical structures. There is no single brain area essential for pain (Apkarian et al., 2005), rather, pain results from activation of a distributed group of structures, some of which are more associated with the sensory-discriminative properties (such as the somatosensory cortex) and others with the emotional aspects (such as the anterior cingulate gyrus and insular cortex) (Basbaum et al., 2009).

Mechanism of nociceptive pain

According to Landa (2012), clinically, pain can be labelled "nociceptive" if it is inferred that the pain is due to on-going activation of the nociceptive system by tissue injury. Although neuroplastic changes, such as those underlying tissue sensitization, are clearly involved, nociceptive pain is presumed to occur as a result of the normal activation of the sensory system by noxious stimuli, a process that involves transduction, transmission, modulation and perception (Figure 1) (AMA, 2010).

Tissue injury activates primary afferent neurones called nociceptors, which are small diameter afferent neurones (with A-delta and C-fibres) that respond to noxious stimuli and are found in skin, muscles, joints and some visceral tissues (Willis, 2007). The fibres have specific receptors that may be responsible for noxious mechanical, chemical or thermal stimuli. One class, called transient receptor potential (TRP) receptors, has been undergoing intensive investigation in the hope of ultimately yielding new therapies for pain (Bevan and Anderson, 2009). The TRPV1 receptor, for example, has been found to be the specific site for reaction to capsaicin, a compound that activates C-fibre nociceptors. Presumably, nociceptive processes linked to noxious events involving somatic or visceral structures begin with activation of these specific receptors, which leads to transduction, the process by which exposure to a sufficient stimulus produces depolarisation of the peripheral nerve (AMA, 2010). There are varying nociceptive primary afferent neurones. Most are "silent", active only when suprathreshold stimuli impinge. Some are specific to one type of stimulus, such as mechanical or thermal, but most are polymodal. The number and size of the receptive fields served by each fibre may be small or large, respectively (AMA, 2010). Nociceptors can also be distinguished according to their differential expression of channels that confer sensitivity to heat (TRPV1), cold (TRPM8), acidic milieu (ASICs) and a host of chemical irritants (TRPA1) (Julius and Basbaum, 2001).

Depolarisation of the primary afferent involves a complex neurochemistry in which substances produced by tissues, inflammatory cells and the neurone itself influence transduction of pain (Landa, 2012). The role of prostaglandins, bradykinin, protons, nerve growth factor and other compounds provide opportunities for the development of new analgesic drugs (AMA, 2010). Once depolarisation occurs, transmission of information proceeds proximally along the axon to the spinal cord and then on to higher centres (Landa, 2012). Complex systems that modulate this input occur at all levels of the neuraxis and are best characterized in the spinal cord. The neuroanatomy, neurophysiology and neurochemistry of these processes are very complex (Stein et al., 2009). Transmission across the first central synapse may be influenced by activity in the primary afferent itself and modulatory neural pathways that originate segmentally or supraspinally; further modulation results from processes initiated by glial cells (Apkarian et al., 2005).

The neurochemistry of the processes involves an extraordinary array of compounds, including endorphins, neurokinins, prostaglandins, biogenic amines, gamma-amino butyric acid (GABA), neurotensin, cannabinoids, purines and many others (AMA, 2010). The endorphinergic pain modulatory pathways are characterized by multiple endogenous ligands and different types of opioid receptors such as: *mu*, *delta* and *kappa*. Endorphins are present in the periphery, on nerve endings, immune-related cells and other tissues, and are widely distributed in the CNS (Landa, 2012). They are involved in many neuroregulatory processes apart from pain control, including the stress response and motor control systems. Opioid drugs mimic the action of endogenous opioid ligands. Most of the drugs used for pain are full *mu* receptor agonists (AMA, 2010); they belong to the G protein-coupled receptor family and signal via a second messenger (cyclic AMP) or an ion channel (K^+) (Gustein and Akil, 2001).

Other pain modulating systems, such as those that use monoamines (serotonin, adrenaline and dopamine), histamine, acetylcholine, cannabinoids, growth factors and other compounds are targets for non-traditional analgesics, such as specific antidepressants and anticonvulsants. It is likely that entirely novel analgesic compounds will become commercially available in the future as drug development programme target these systems (Woolf, 2004). Nociceptive pain may involve acute or chronic inflammation. The physiology of inflammation is complex. In addition to an immune component, retrograde release of substances from C polymodal nociceptors also may be involved (Landa, 2012). This "neurogenic inflammation" involves the release from nerve endings of compounds such as substance P, serotonin, histamine, acetylcholine and bradykinin. These substances activate and sensitize other nociceptors. Prostaglandins produced by injured tissues also may enhance the nociceptive response to inflammation by lowering the threshold to noxious stimulation (AMA, 2010).

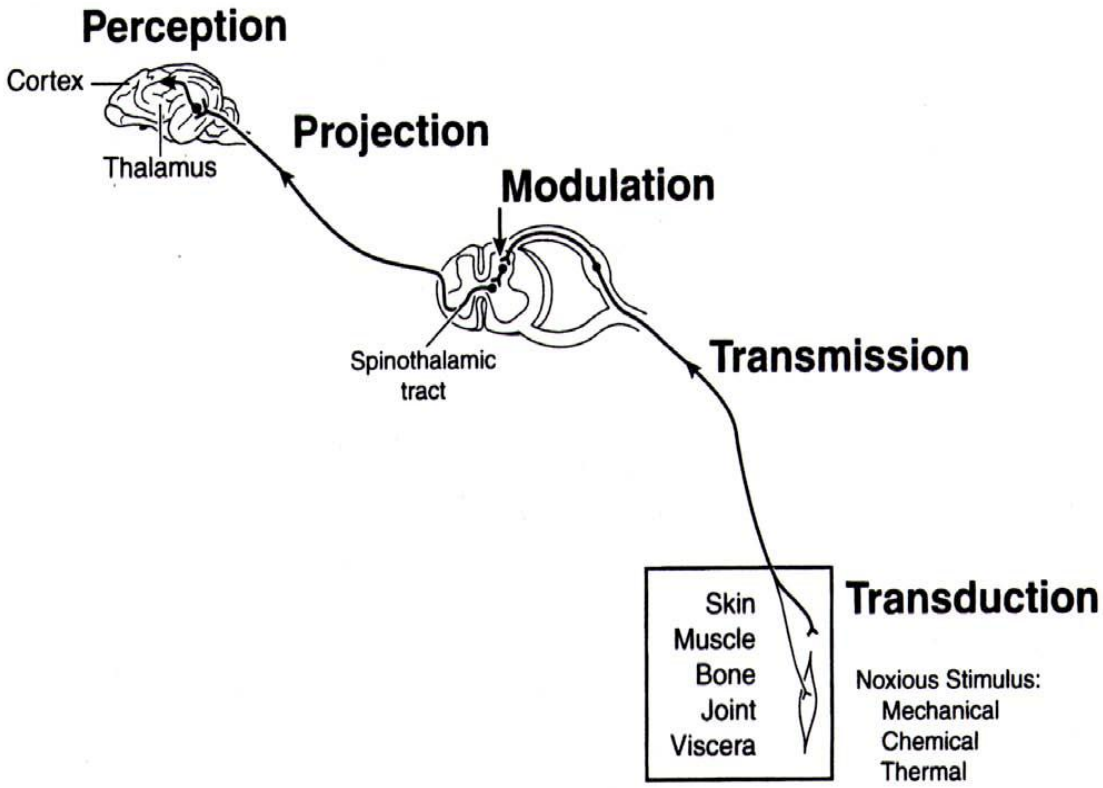

Figure 1. A schematic diagram of pain process. Source: Alvin (2006).

Mechanism of neuropathic pain

Neuropathic pain is the label applied to pain syndromes inferred to result from direct injury or dysfunction of the peripheral nervous system or CNS. These changes may be caused by injury to either neural or non-neural tissues. Although neuropathic pain may be strongly influenced by on-going tissue injury or other stimuli that activate the sensory system, there is an assumption that the fundamental mechanisms sustaining the pain may become independent of any on-going tissue injury (Jarvis and Boyce-Rustay, 2009). Although representing a gross over-simplication of very complex processes, it may be valuable to sub-classify neuropathic pain syndromes, based on additional inferences of the primary location of the sustaining mechanisms (Portenoy, 1999). Some of the neurophysiologic and neuroanatomic changes that may occur in peripherally-generated neuropathic pain have been elucidated (Truini and Cruccu, 2006).

Injury to a peripheral nerve axon can result in abnormal nerve morphology. The damaged axon may grow multiple nerve sprouts, some of which form neuromas. These nerve sprouts, including those forming neuromas, can generate spontaneous activity, which peaks in intensity several weeks after injury. These areas of increased sensitivity are associated with a change in sodium receptor concentration and other molecular processes. They can occur at sites of demyelination or nerve fibre injury not associated with the severing of axons (Landa, 2012). Unlike normal nerve, these injured regions are more sensitive to physical stimuli, which is clinically associated with tenderness and the appearance of Tinel's sign (that is pain or tingling when the area over a nerve is tapped). After a period of time, atypical connections may develop between nerve sprouts or demyelinated axons in the region of the nerve damage, permitting "cross-talk" between somatic or sympathetic efferent nerves and nociceptors (Landa, 2012).

Other changes occur in peripheral nerve that are related to pain and yet poorly characterized. Anterograde and retrograde transport of compounds may shift and messages that are received in cell bodies may turn on specific genes. More proximally, there are identifiable trans-synaptic changes. Some of these alterations in morphology and function result in peripheral sensitisation, which may be related to a lower threshold for signalling or an expansion in receptive fields. Functional neuro-imaging has demonstrated the extraordinary neuroplasticity

of the brain in the setting of a neuropathic pain, such as phantom pain, but the mechanisms responsible are unknown (Bingel and Tracey, 2008).

Mechanism of psychological and "idiopathic" pain

There is an exceedingly complex relationship between the psyche and pain perception (Gamsa, 1994). In some patients, the experience of persistent pain appears to induce disturbances in mood (reactive depression or anxiety), impaired coping (often with catastrophization) and other processes, which in turn appear to worsen pain and pain-related distress. Other patients have pre-morbid or co-morbid psycho-social concerns or psychiatric disorders that are best understood as evolving in parallel to the pain. These disturbances also can contribute to the pain experience and driver pain-related distress. Patients with personality disorders, substance-use disorders or mood disorders often are best served by primary treatment for the psychiatric problem at the same time that pain-related interventions are offered. This array of pre-morbid, co-morbid and reactive psychosocial disturbances is individual and complex, and may occur in a shifting mix of primary and secondary concerns (Landa, 2012). On occasion, the psychological evaluation yields evidence that the pain itself is predominantly sustained by psychological factors. This phenomenon is known generically as "psychogenic" pain, and is subject to the specific diagnoses codified under the Somatoform Disorders in the Diagnostic and Statistical Manual of the American Psychiatric Association (Frances et al., 2000).

PAIN RECOGNITION AND ASSESSMENT

Humans and animals have common anatomical and physiological features which have given rise to why animal pain is so often ignored. The answer to this question may be due to the fact that the ability to assess pain in farm animals is still very limited. However, the inability to fully recognize pain does not mean that it does not exist. This is particularly true for ruminants in which concealment of vulnerability and weakness appears to be adaptive (Broom, 2001; Weary et al., 2006). This conclusion is based on numerous studies providing strong scientific support based on behavioural and physiological indicators of pain measured as part of the assessment (Stafford and Mellor, 2005; Coetzee, 2011).

PHYSIOLOGICAL RESPONSES TO PAIN

The main glucocorticoid hormone that is released in response to stresses, including pain, is cortisol (Hecter and Pincus, 1954; Weary et al., 2006). The corticosteroid level can be measured in plasma or saliva and is a widespread means for the physiological assessment of the activity of the hypothalamus-pituitary-adrenal axis, which is activated in painful conditions (Molony and Kent, 1997). Cortisol measurement has been used in animals to estimate the effects of different painful procedures such as abdominal surgery (Pearson and Mellor, 1975), electro-immobilisation (Jephcott et al., 1986, 1987) and castration (Mellor and Murray, 1989). Samples of blood are usually collected from the jugular vein and for estimation of cortisol levels by radioimmunoassay (RIA) (Shutt et al., 1988; Mellor and Murray, 1989; Graham et al., 1997).

Plasma cortisol levels in groups of animals undergoing painful stimulation are compared with control groups of animals which are without pain and just handled. Weary et al. (2006) noted that measurements of physiological parameters often require the restraint of animals and tissue sampling, which can be stressful and may influence the results. Despite these caveats, the assessment of plasma cortisol levels remains a well-proven and common method for pain evaluation, which include plasma determination of concentration of adrenocorticotropin hormone, glucose and lactate (Prunier et al., 2005; Mormede et al., 2007; Keita et al., 2010). Prunier et al. (2005) used lactate measurements to reveal the metabolic processes taking place during pain. Catecholamines are produced in response to stressful events (including pain), and this result in an increase in glycogenolysis and mobilisation of glycogen, predominantly from muscle tissue, and as a consequence an increase in lactate and glucose production. In addition to cortisol parameters, Shutt et al. (1988) and Mears and Brown (1997) used changes in plasma immunoreactive beta-endorphin as an indicator of pain by means of RIA. Attempts have also been made to connect pain (caused by castration of male pigs) with fluctuations in the levels of tumour necrosis factor alpha, interleukin-1beta, C-reactive protein, serum amyloid A and haptoglobin in blood; however, no changes in the levels of these substances were revealed (Moya et al., 2008).

Conclusion

Pain control and management is an important welfare concern even in routine management procedures of livestock. Adequate knowledge and understanding of its mechanisms and physiologic responses in animals may serve as an aid to its efficient management and consequently, increased livestock production.

Conflict of Interests

The author(s) have not declared any conflict of interest.

REFERENCES

Alvin B (2006). Nociception1_06.ppt. Schematic diagram of the pathway of physiologic pain. (Accessed on 18th May, 2012).

American Medical Association (2010). Pain management and drug prescription.

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK (2005). Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9(4):463-484.

Basbaum AI, Jessell T (2000). The perception of pain. In: Kandel ER, Schwartz J, Jessell T (eds.), Principles of Neuroscience. New York: Appleton and Lange. pp. 472-491.

Basbaum AI, Baustita DM, Scherrer G, Julius D (2009). Cellular and molecular mechanisms of pain. Cell 139(2):267-284.

Bayvel ACD (2004). Global Conference on Animal Welfare: An OIE initiative. OIE Animal Welfare Strategic Initiative: Progress, Priorities And Prognosis. World Organization for Animal Health, Paris. pp. 13-23.

Bevan S, Anderson DA (2009). TRP channel antagonists for pain-Opportunities beyond TRPV1. Curr. Opin. Investig. Drugs 10(7):655-663.

Bingel U, Tracey I (2008). Imaging CNS modulation of pain in humans. Physiology 23:371-380.

Braz JM, Nassar MA, Wood JN, Basbaum AI (2005). Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor. Neuron 47:787-793.

Broom DM, Fraser AF (2007). Domestic Animal Behaviour and Welfare, 4th Ed. CABI Publishing, Wallington, UK. pp. 61-62.

Broom DM (2001). Evolution of pain. In: Soulsby L, Morton, D. (Eds.), Pain - Its Nature and Management in Man and Animals. The Royal Society of Medicine Press, London, UK. pp. 17-25.

Coetzee JF (2011). A review of pain assessment techniques and pharmacological approaches to pain relief after bovine castration: Practical implications for cattle production within the United States. Appl. Anim. Behav. Sci. 135:192-213.

Carroll GL (2009). Small Animal Anesthesia and Analgesia. Ames, IA: Wiley-Blackwell. P 65.

Faries FC (2010). Pain Recognition. American Extension Veterinary Medicine (AEVM). http://aevm.tamu.edu/files/2010/07/Pain_Recognition_11.pdf (Accessed on 25th May, 2011).

Frances A, Pincus HA, First MB (2000). Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association. pp. 498-503.

Frandson RD, Wilke WL, Fails AD (2009). Anatomy and Physiology of Farm Animals, 7th ed. Wiley-Blackwell, Iowa. P 528.

Flecknell P (2000). Animal Pain–an introduction. In: Flecknell P, Waterman-Pearson A (Eds.), Pain Management in Animals. WB Saunders Co, London, UK. pp. 1-8.

Gamsa A (1994). The role of psychological factors in chronic pain. A half century of study. Pain 57(1):5-15.

Giamberardino MA, Vecchiet L (1997). Pathophysiology of visceral pain. Curr. Pain Headache Rep. 1:23-33.

Gleed RD, Ludders JW (2008). Analgesia. In: Gleed RD, Ludders JW (Eds.), Recent Advances in Veterinary Anesthesia and Analgesia: Companion Animals. International Veterinary Information Service, Ithaca NY (www.ivis.org).

Campoy L (2005). Fundamentals of regional anesthesia using a peripheral nerve stimulator. In: In: Gleed RD, Ludders JW (Eds.), Recent Advances in Veterinary Anesthesia and Analgesia: Companion Animals. http://www.anestesia.vet.br/distribution/download/file.php?id=25 Accessed 2nd March, 2012.

Graham MJ, Kent JE, Molony V (1997). Effects of four analgesic treatments on the behavioural and cortisol responses of 3-week-old lambs to tail docking. Vet. J. 153:87-97.

Gustein HB, Akil H (2001). Opioid analgesics. In: Hardman JG, Limbird LL (eds.), Goodman and Gilman's Pharmacological Basis of Therapeutics. New York: McGraw-Hill. pp. 569-619.

Hecter O, Pincus G (1954). Genesis of the adrenocortical secretion. Physiol. Rev. 34:459-496.

Heller P, Rodan I, Robin D (2007). AAHA/AAFP pain management guidelines for dogs and cats. J. Am. Anim. Hospit. Assoc. 43:235-248.

Henke J, Erhardt W (2001). Schmerzmanagement bei Klein- und Heimtieren. Enke Verlag, Stuttgart. P 135.

International Association for the Study of Pain (2012). Part III: Pain Terms, A Current List with Definitions and Notes on Usage. In: Merskey H, Bogduk N (eds.), IASP Task Force on Taxonomy. IASP Press, Seattle, USA. pp. 209-214.

Jarvis MF, Boyce-Rustay JM (2009). Neuropathic pain: models and mechanisms. Curr. Pharm. Des. 15(15):1711-1716.

Joshi SK, Gebhart GF (2000). Visceral pain. Curr. Rev. Pain 4:499-506.

Jephcott EH, McMillen IC, Rushen J, Hargreaves A, Thornburn GD (1986). Effect of electro-immobilisation on ovine plasma-concentrations of beta-endorphin/beta-lipotrophin, cortisol and prolactin. Res. Vet. Sci. 41:371-377.

Jephcott EH, McMillen IC, Rushen J, Thornburn GD (1987). A comparison of electro-immobilization and/or, shearing procedures on the ovine plasma concentrations of beta-endorphin/beta-lipotrophin. Res. Vet. Sci. 43:97-100.

Julius D, Basbaum AI (2001). Molecular mechanisms of nociception. Nature 413(6852):203-210.

Kamerling SG (1993). Narcotics and local anaesthetics. Vet. Clin. North Am. Equine. Pract. 9:605-620.

Keita A, Pagot E, Prunier A, Guidarini C (2010). Pre-emptive meloxicam for post-operative analgesia in piglets undergoing surgical castration. Vet. Anaesth. Analg. 37:367-374.

Lamont LA, Tranquilli WJ, Grimm KA (2000). Physiology of pain. Vet. Clin. North Am. Small Anim. Pract. 30(4):704-753.

Landa L (2012). Pain in domestic animals and how to assess it: a review. Vet. Med. 57(4):185-192.

Leung L, Cahill CM (2010). TNF-alpha and neuropathic pain-a review. J. Neurol-infl. 7:7-27.

Loeser JD, Treede RD (2008). The Kyoto protocol of IASP Basic Pain Terminology. Pain 31:137(3) 473-477.

Malmberg AB, Chen C, Tonegawa S, Basbaum AI (1997). Preserved acute pain and reduced neuropathic pain in mice lacking PKC gamma. Science 278:279-283.

McMahon SB, Dimitrieva N, Koltzenburg M (1995). Visceral pain. Br. J. Anaesth. 75:132-144.

Mears GJ, Brown FA (1997). Cortisol and beta-endorphin responses to physical and psychological stressors in lambs. Can. J. Anim. Sci. 77:689-694.

Mellor DJ, Murray L (1989). Effects of tail docking and castration on behaviour and plasma cortisol concentrations in young lambs. Res. Vet. Sci. 46:387-391.

Merskey H (1979). Pain terms: a list with definitions and a note on usage. Recommended by the International Association for the Study of Pain (IASP) Subcommittee on Taxonomy. Pain 6:249-252.

Meyer RA, Ringkamp M, Campbell JN, Raja SN (2008). Peripheral mechanisms of cutaneous nociception. In: McMahon SB, Koltzenburg M (eds.), Wall and Melzack's Textbook of Pain. Philadelphia: Elsevier. pp. 3-34.

Mogil JS, Crager SE (2004). What should we be measuring in behavioral studies of chronic pain in animals. Pain 112:12-15.

Molony V, Kent JE (1997). Assessment of acute pain in farm animals using behavioural and physiological measurements. J. Anim. Sci. 75:266-272.

Moya SL, Boyle LA, Lynch PB, Arkins S (2008). Effect of surgical castration on the behavioural and acute phase responses of 5-day-old piglets. Appl. Anim. Behav. Sci. 111:133-145.

Mormede P, Andanson S, Auperin B, Beerda B, Guemene D, Malnikvist J, Manteca X, Manteuffel G, Prunet P, Van Reenen CG, Richard S,

Veissier I (2007). Explorations of the hypothalamic-pituitary-adrenal function as a tool to evaluate animal welfare. Physiol. Behav. 92:317-339.

Neumann S, Braz JM, Skinner K, Llewellyn-Smith IJ, Basbaum AI (2008). Innocuous, not noxious, input activates PKC gamma interneurons of the spinal dorsal horn via myelinated afferent fibers. J. Neurosci. 28:7936-7944.
Paine P, Kishor J, Worthen SF, Gregory LJ, Aziz Q (2009). Exploring relationships for visceral and somatic pain with autonomic control and personality. Pain 144:236-244.
Pearson RA, Mellor DJ (1975). Some physiological changes in pregnant sheep and goats before, during and after surgical insertion of uterine catheters. Res. Vet. Sci. 19: 102-104.
Portenoy RK (1999). Issues in the management of neuropathic pain. In: Basbaum AI, Besson JM (eds.), Towards a New Pharmacotherapy of Pain. Chichester, UK: John Wiley & Sons. pp. 393-416.
Prunier A, Mounier A, Hay M (2005). Effects of castration, tooth resection, or tail docking on plasma metabolites and stress hormones in young pigs. J. Anim. Sci. 83:216-222.
Robertson SA (2002). Pain management in laboratory animals-are we meeting the challenge. J. Am. Vet. Med. Assoc. 221:205-208.
Shutt DA, Fell LR, Connel R, Bell AK (1988). Stress responses in lambs docked and castrated surgically or by the application of rubber rings. Austr. Vet. J. 65:5-7.
Smith HS, Pappagallo M (2013). Essential Pain Pharmacology: The Prescriber's Guide. Anesthesiology 119(4):997-998.
Stafford KJ, Mellor DJ (2005). The welfare significance of the castration of cattle: A review, New Zealand. Vet. J. 53:271-278.
Stein C, Clark JD, Oh U (2009). Peripheral mechanisms of pain and analgesia. Brain Res. Rev. 60(1):90-113.
Stillwell G (2009). Pain evaluation and control after routine interventions in cattle. Tese de doutoramento em ciências veterinárias. pp. 43-55.
Truini A, Cruccu G (2006). Pathophysiologic mechanisms of neuropathic pain. Neurol. Sci. 27(2):179-182.
Vinuela-Fernandez I, Jones E, Welsh EM, Fleetwood-Walker SM (2007). Pain mechanisms and their implication for the management of pain in farm and companion animals. Vet. J. 174:227-239.
Weary DM, Niel L, Flower FC, Fraser D (2006). Identifying and preventing pain in animals. Appl. Anim. Behav. Sci. 100:64-76.
Willis WD (2007). The somatosensory system, with emphasis on structures important and notes on usage. Pain 6:249-252.
Woolf CJ (2004). Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Ann. Intern. Med. 140:441-451.