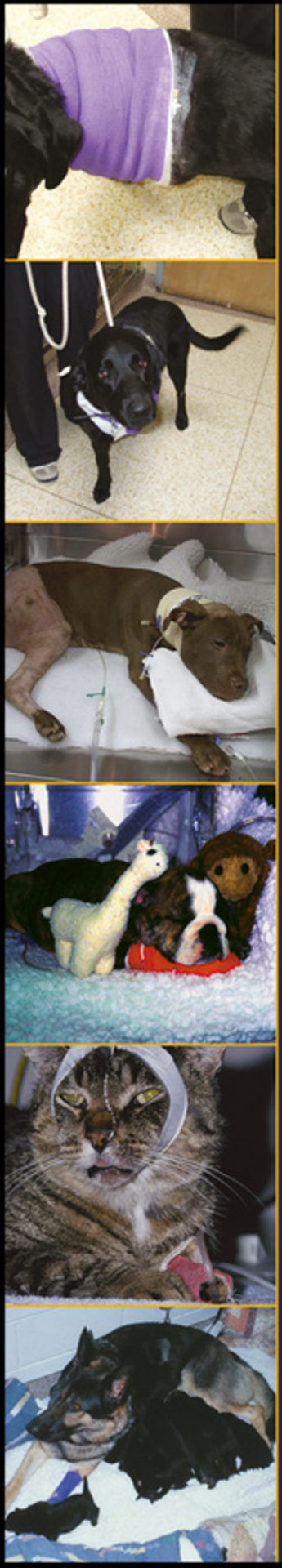

Analgesia and Anesthesia for the Ill or Injured Dog and Cat

Karol A. Mathews
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WILEY Blackwell

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Preface

All injured, and many ill, patients are in pain, but deciding on how painful the patient is, and the best pain management strategy for many, can be challenging. General considerations for pain management upon presentation are detailed and, as many patients will require anesthesia to manage their problem or to facilitate further diagnostics, basic information gathering is also outlined. Selecting an appropriate, safe analgesic and anesthetic regimen can be difficult, compounded by the anatomical location involved and associated co-morbidities. This book addresses these concerns, detailing pharmacologic and physiologic mechanisms applicable to groups (pregnant, nursing, pediatric, geriatric) and etiologies of pain. In addition to a step-by-step approach through various scenarios based on anatomical location of illness or injury, the veterinary technician/nurse's role in managing these patients, and the methods of analgesic delivery, are detailed.

Acknowledgements

While the authors have years of experience managing ill or injured cats and dogs, specific details of a colleague's practice, or publications, were sought and shared. For their contribution, we would like to thank: Drs. Alexa Bersenas, Alice Defarges, Robin Downing, Mark Epstein, Steve Escobar, Bernard Hansen, Fiona James, Mark Papich, Bruno Pypendop, Marc Raffe, Margie Scherk, Kelly St. Denis, Bob Stein and Bonnie Wright.

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For pharmaceutical assistance and researching details of usage, global availability, approval of veterinary analgesics and government controls, we would like to thank Heather Kidston, RPh, FSVHP, Pharmacy Manager, Ontario Veterinary College Health Sciences Centre, University of Guelph, Guelph, Ontario, Canada. We would also like to thank Greg Soon BSc(Pharm), Pharmacist – ICU, Peterborough Civic Hospital, Ontario, Canada for his assistance in contributing publications and specific details on human-only-approved analgesics used in various scenarios in this book.

Where specific information is not available in the veterinary literature, we would like to thank Lorne Porayko MD, FRCP(C), CIM Consultant in Critical Care Medicine & Anaesthesiology, Victoria, BC, Canada, for sharing the information available for humans, and his experiences with some aspects, which are incorporated for human comparison into the various topics.

1

General Considerations for Pain Management upon Initial Presentation and during Hospital Stay

Karol Mathews

The quest for relief from pain is pursued in human medicine because its existence is known since the patient can verbalize their pain: what it feels like, where it is and the relief they feel when treatment is appropriate. As we all have experienced pain of various degree and duration, it is an excellent topic for comparison and understanding with our veterinary patients. As veterinary patients cannot tell us how painful they are, we as veterinarians and veterinary technicians/nurses have to understand what can cause pain and how pain manifests itself, which is discussed throughout this book, and how best to treat it.

Upon presentation immediate and appropriate treatment for the presenting problem should begin. Managing these problems frequently relieves some of the pain experienced (e.g. cooling a burn). The analgesic procedures are included in the scenarios; however, for definitive management of the presenting problem, the reader is referred elsewhere. Initial management is also based on inclusion/exclusion of pre-existing problems, medications and when the patient was last fed. An additional factor is the aggressive nature of the patient and how to deal with that (Chapter 22). Frequently, patients require diagnostic imaging and some may require surgical management. Specific analgesic/anesthetic protocols will be required for each circumstance. Preparation for intubation and assisted ventilation is essential. As cardiac arrhythmias may occur within 12–24 h (if not already present) following trauma, continuous ECG monitoring must be included in the ongoing patient assessment.

While management procedures contribute to a reduction in the pain experienced, analgesics are an essential component of case care in the urgent and emergent trauma, and for many critically ill, patients. Some degree of inflammation is present in these patients and is associated with great energy expenditure, the demands for which frequently cannot be met. The addition of pain, a great utilizer of energy, can contribute to associated morbidity, especially in the more seriously affected patients. In addition to the pain experienced by the primary problem, there is an additive effect of pain due to placement/presence of IV, urinary, thoracic, abdominal catheters and drains. Many undergo frequent manipulations and procedures that contribute to the overall pain experienced. Prior to analgesic and anesthetic selection, the pharmacologic aspects and contraindications for the various agents must be considered due to the fragile organ function of many of our ill or injured patients. Refer to the pharmacology and clinical application of sedatives (Chapter 9), opioids (Chapter 10), non-steroidal anti-inflammatory analgesics (Chapter 11), adjunct analgesia (Chapter 12) and anesthetics (Chapter 13). As pain is an individual experience associated with specific situations, general dosing of analgesics may not be appropriate. Refer to Chapter 8 for analgesic dosing suggestions for various levels of pain and the individual scenario chapters.

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A common misconception is that analgesics mask physiological indicators of patient deterioration (e.g. tachycardia in response to hypotension) and are, therefore, withheld. Evidence to support that analgesics *do not* mask signs of patient deterioration is reported in both the human and veterinary literature [1]. In fact, improved outcomes of well-managed pain in trauma patients is reported [2]. Our clinical observations show that when opioids are administered as a slow push or as a continuous rate infusion to treat pain an appropriate heart rate in response to hypotension, hypoxia, hypovolemia or hypercarbia still occurs. As tachycardia frequently occurs in the painful patient, treating the pain and eliminating this component as a cause for tachycardia, the persistence or recurrence of increased heart rate alerts the clinician to potential patient deterioration. If appropriate analgesia is not administered, tachycardia may be assumed to be pain and not patient deterioration. It is essential to obtain intravenous (IV) access, collect blood for laboratory evaluation and commence fluids while initiating opioid analgesia. Where hemorrhage or other hypovolemic states may exist, the severity of intravascular volume loss may be masked by the pain-induced "artificial" blood pressure (BP) reading. With administration of an analgesic, the pain-induced sympathetic response is reduced, allowing the BP reading to reflect the true intravascular volume. Heart rate will still reflect volume loss. Studies confirm that opioids do not result in a deterioration in hemodynamics when administered to dogs with 30% blood loss. Should BP drop below normal during opioid administration, this reflects that hypovolemia and fluid administration should be increased to that required for the patient. Where blood loss is identified, continuous monitoring of BP and laboratory evaluation is essential to identify the patient requiring a blood transfusion. The biochemistry results will identify organ dysfunction and will assist with selection of an analgesic protocol—and an anesthetic protocol should this be required.

Another concern expressed by many veterinarians is the potential for adverse reactions associated with analgesic drug administration, especially so for cats. However, current evidence, based on many studies investigating the efficacy and tolerability of analgesics of several drug classes, indicates that adverse effects are minimal when used appropriately [3]. This applies to both cats and dogs [4]. Adverse effects, primarily those associated with opioid use, such as respiratory depression, are extrapolated from humans and are over-emphasized in dogs and cats. In thirty years of practice in the critical care setting, this author has witnessed only two such incidences, both associated with fentanyl patch application in very small dogs. With respect to ventilation, opioid administration after a traumatic incident frequently improves ventilation rather than impairs it. This has been confirmed by arterial blood gas assessment by the author. Based on the physiologic abnormalities present in the ill or injured cat and dog, selection, dosing and method of administration of analgesics require careful consideration to ensure efficacy without the potential for adverse effects. As an example, non-steroidal anti-inflammatory analgesics (NSAIAs) should never be administered to any ill or injured patient upon presentation (Chapter 11). The administration of NSAIAs in the emergent patient should be withheld until the volume, cardiovascular, liver and kidney status of the patient is determined to be within normal limits and there is no potential for deterioration, such as ongoing or occult hemorrhage. Human patients with severe or poorly controlled asthma, or other moderate to severe pulmonary disease, may deteriorate with **cyclooxygenase 1 (COX-1) selective NSAIA** administration [5]. It is not known whether this may occur in cats and dogs; however, as bronchodilator physiology is similar across species, this may still be a concern. As asthmatic patients receive glucocorticoid therapy, NSAIA would be contraindicated. COX-1 selective NSAIAs are not recommended for any patient scenario included in this book.

Concerns for opioid immunosuppressive effects, and subsequent infection, have been reported in the human literature. Based on the author's experience working with critically ill patients all receiving opioids, infections potentially associated with opioid use were not identified. However, as the immunosuppressive potential of some opioids, especially morphine, was

raised [6], a two-month prospective study was carried out at the author's institution, including all patients (ICU and surgical ward) with a variety of problems receiving opioids. Fentanyl, hydromorphone and buprenorphine were opioids used predominantly, in addition to NSAIAs, which demonstrated a 6/140 (4.3%) new infection rate. Survival rate was 98% with 2% euthanasia due to poor prognosis (e.g. neoplasia, severe head trauma). As with other reported studies, the tibial plateau levelling osteotomy (TPLO) procedure was the major orthopedic procedure represented in the infection rate (two of the six patients acquiring infections). Interestingly, critically ill patients rarely acquired infection, whereas the TPLO procedure is performed in healthy dogs. An earlier study investigating surgical site infections (SSIs) in dogs at the same institution receiving opioids during hospitalization included 846 dogs over a 45-week period and identified 26 (3%) SSIs [7]. A recent study in healthy dogs reported that morphine and buprenorphine did not alter leukocyte production, early apoptosis or neutrophil phagocytic function [8]. It is important to add that pain, and associated stress, is immunosuppressive and the withholding of analgesics based on a potential problem may increase morbidity rather than prevent it. In addition, the effect of hospitalization alone on the stress response in cats [9] and dogs [10, 11] has been described and this stress could have profound effects on the immune system [12], especially when associated with trauma [13]. Pain will compound this stress, illustrating the importance of appropriate analgesia [14].

Many ill or injured animals will require diagnostic and emergency procedures where analgesia, to facilitate restraint, is essential. As each animal will present with varying levels of injury or illness and experience different levels of pain, one cannot apply a standard regimen for all patients. An opioid is the analgesic of choice for initial management; however, dose and method of administration is patient- and situation-dependent and is described in the individual scenarios in this book. In the immediate post-traumatic event, the stress response may reduce the pain experienced below that expected for the associated injury. Therefore, bolus administration of analgesics is not advised due to the potential for adverse effects (panting, nausea, vomiting, dysphoria) when the amount administered is excessive for the degree of pain experienced. "A single dose does not fit all"; therefore, titration to effect is essential. The opioid requirement can be increased as the "stress analgesic response" diminishes. Other important considerations are all drug interactions within the patient and drug compatibilities within the infusions. Refer to Chapter 9 for more detail on sedatives, Chapter 10 (opioids), Chapter 11 (NSAIAs), Chapter 12 (adjunct analgesia), Chapter 13 (anesthetics) and Chapter 18 (preparation and delivery of analgesics).

The aggressive patient will require a different approach and this is patient- and situation-dependent. Patients may be aggressive upon presentation from pain and fear, or may be aggressive in a strange environment. Animals may appear to be stable when acting aggressively upon admission; however, endorphin and epinephrine release can mask the seriousness of the patient's clinical condition. Chemical restraint rather than force is the humane and often safer way to deal with these animals. Assess the patient from afar and, where time permits, obtain a thorough history, including potential current drug therapy, before selecting a method of restraint. Once the reason for the aggression has been identified, frequently associated with significant pain and fear in traumatized animals, a more direct approach to management can follow. Details and drugs/dosages are given in Chapter 22. Respiratory distress may appear as a combination of panic and aggression; therefore, provide "flow by" oxygen initially as this will relieve some stress. If possible, use an open mask (without the diaphragm) to concentrate oxygen towards the nose of the cat or dog, but without touching the face. As soon as possible following sedation, place two or three drops of ophthalmic local anesthetic drops (e.g. proparacaine) into the entry of the nasal passages, then five minutes later place nasal cannulae (prongs, Figure 1.1) or nasal catheter in the dog. For smaller dogs, use an oxygen cage, if available, immediately following sedation. Cats may be better oxygenated in an induction

Figure 1.1 Placement of nasal cannulae following placement of 2–3 drops of ophthalmic local anesthetic.

chamber, an oxygen hood or a cage; administer an analgesic intramuscular prior to placing in the oxygen rich environment if possible. Refer to Chapter 28 for details.

Of utmost importance to consider is that a continual painful experience is detrimental to the overall well-being and healing process of humans and animals, resulting in prolonged hospital stay, which increases the potential for secondary problems such as hospital-associated infections. Another potential outcome in veterinary patients is euthanasia due to increasing costs. Also of importance is the association between inadequately treated acute pain and the development of chronic pain. This has been reported in human patients occurring after traumatic, surgical and painful medical conditions [2]. While considering all the negative physiological effects associated with the experience of pain, above all, inadequate analgesia resulting in ongoing pain is inhumane.

It is important to question the owner about pre-existing co-morbidities as cardiovascular, hepatic and renal problems will influence the pain and anesthetic management protocol. It is also important to enquire as to pre-existing orthopedic problems (e.g. osteoarthritis of various joints) as careful handling or manipulation of these areas in general, and whilst under general anesthesia for diagnostic purposes, is essential to avoid increasing the degree of pain.

General anesthetics (inhalant, propofol, barbiturates) may be required for surgical or diagnostic procedures for any ill or injured patient and the approach to prevention of pain applies to all. Special considerations for the individual patient are required (refer to Chapter 13 for details and the scenarios in this book for guidance). It is important to note that general anesthetics only block conscious perception of pain for the duration of anesthesia; however, nociceptive input still occurs and will be experienced by the patient upon recovery. Ketamine, however, has anti-hyperalgesic and analgesic properties. The practice of "preventive" analgesia is to reduce the impact of the total peripheral nociceptive barrage associated with noxious pre-, intra- and post-operative or traumatic stimuli [11]. The term "preemptive analgesia" is restricted to analgesic administration prior to the onset of pain, such as in the pre-operative setting with the intention of reducing nociceptive input and potential peri-operative pain. However, this single event of analgesic administration is inadequate to manage post-operative, and frequently intraoperative, pain. Where moderate to severe pain is to be expected, and is frequently associated with injured and some ill patients, one or more classes of analgesics (based on pain severity) with a demonstrated preventive effect should be administered in addition to an opioid. These analgesics (NSAIAs, local anesthetics, N-methyl-D-aspartate (NMDA) antagonists (e.g. ketamine)) not only reduce the inhalant requirement (MAC reduction) and

severity of acute post-surgical pain but may in some cases also reduce the incidence of chronic (persistent) post-operative pain. The efficacy of a multi-modal regimen, combining drugs with pharmacologic action at different sites in the pain pathway, provides optimal analgesia to treating pain, while reducing the dosage of each drug and, therefore, reducing the potential for adverse effects of any single drug that would otherwise require high dosing. Of utmost importance is the utilization of neuraxial analgesia and local blocks wherever possible, both intraoperatively and post-operatively (refer to Chapter 14 for details on the application of all potential techniques for the individual patient). As pain transmission is complex, all nociceptive pathways must be blocked to effect optimal analgesia [15] (refer to Chapter 2). Refer to the pharmacology and clinical application of sedatives (Chapter 9), opioids (Chapter 10) and adjunct analgesia (Chapter 12) for further details.

Illness or injury results in an inflammatory response either local to the area involved or systemically. The presence of inflammation increases the degree of pain experienced following a surgical procedure when compared to that of a routine procedure. As an example, ovariohysterectomy in patients with metritis or pyometra will require higher dosing of analgesics during and after ovariohysterectomy and for longer duration when compared to that of a routine elective procedure. Also, in addition to the potential establishment of chronic pain due to inadequate pain management, inadequately treated pain associated with abdominal or thoracic incisions prevents normal ventilation/oxygenation. Controlled walking and other rehabilitation exercises are essential for post-operative orthopedic repair to ensure appropriate "stress" for bone healing, enhance periosteal blood flow and to maintain muscle mass to support the limb. Without adequate analgesic administration, frequently requiring at least two classes of analgesics, movement will be too painful, resulting in non-use bone and muscle atrophy. Above all, "facilitating pain" to control movement following surgery is unethical. When in hospital, controlled leash walking and integrative techniques (refer to Chapter 15) should be included in the post-operative management protocol, neither of which can be tolerated when in pain. Similar discharge home instructions, with analgesia, must be given.

When considering analgesic selection, the adverse effects must be minimal due to the fragile organ function of these patients. Other important considerations are drug interactions within the patient. Drug metabolism and clearance is primarily via the liver and kidney; where a patient is identified with organ dysfunction, an NSAIA is contraindicated. However, opioid analgesics can still be administered. Initial dosing to effect is required to reach therapeutic levels; however, the dosing intervals may be extended and the hourly infusion rates may be reduced based on patient assessment as the metabolism and excretion may be reduced. The ongoing dosing with adjustments will be dependent on the individual patient. To optimize efficacy and safety, evaluation of cardiovascular, hepatic respiratory and renal systems is essential to guide ongoing pain management. Refer to the appropriate chapters (Chapter 19, cardiovascular; Chapter 20, kidney; and Chapter 21, liver) for information on drug metabolism and excretion, and adjustments in the delivery regimen, for patients with significant organ dysfunction (refer to Chapter 18).

Pregnant (Chapter 23), nursing (Chapter 24) and pediatric (Chapter 25) patients may present with an injury or illness associated with various degree of pain, which must be managed to prevent the consequences noted above. Of importance, is that the newborn and infant animals feel pain and, in fact, have increased sensation when compared to a similar stimulus in an adult. It is extremely important to prevent/treat pain in these patients as permanent hyperalgesia/allodynia may manifest due to the extreme plasticity of the central nervous system in these young animals.

Sedation must not be interpreted as analgesia; therefore, midazolam or dexmedetomidine should only be used as adjuncts in addition to analgesics for stable patients requiring more "restraint" or sedation than the analgesic alone can provide. Refer to Chapter 9 for details.

Figure 1.2 A clean, warm and comfortable environment reduces stress and, therefore, pain.

Of great importance is that analgesia should be withdrawn slowly to avoid an abrupt return to a hyperalgesic state should pain still be present. Where the recurrence of pain is identified, return to the previous dose for several more hours and attempt withdrawal very slowly when appropriate.

Analgesia and sleep is the goal; therefore, it is essential that optimal patient care be provided to avoid further pain (Figure 1.2) and stress. Based on the anxiety and stress our patients experience whilst in the hospital and the detrimental effect this has on their well-being and recovery, it is essential that the nursing care described in Chapter 17, and in all the scenarios presented, is implemented. The requirement for ongoing analgesia is the dual responsibility of the veterinary technician/nurse and the veterinarian and is outlined in Chapter 16. The analgesic/sedative and anesthetic regimen must be tailored to the individual patient according to the problem at hand. See suggestions and recommendations for individual case scenarios throughout this book and review other chapters to optimize analgesic and anesthetic management.

To complete the picture of managing pain in all conditions in small animal practice, consult references [4] and [16].

References

1 Brock, N. (1995) Treating moderate and severe pain in small animals. *Can Vet J*, 36: 658–660.

2 Randall, J., Malchow, M. D., Black, I. H. (2008) The evolution of pain management in the critically ill trauma patient: Emerging concepts from the global war on terrorism. *Crit Care Med*, 36: S346–S357.

3 Robertson, S. A. (2008) Managing pain in feline patients. *Vet Clin North Am Small Anim Pract*, 38: 1267–1290.

4 Mathews, K. A., Kronen, P. W., Lascelles, D. X., *et al*. (2014) WSAVA: Global Pain Council Guidelines for Recognition. *Assessment and Treatment of Pain in Small Animals*, 55(6): E10–E68.

5 Jenkins, C. (2000) Recommending analgesics for people with asthma. *Am J Ther*, 7(2): 55–61.

6 Odunayo, A., Dodam, J. R. and Kerl, M. E. (2010) Immunomodulatory effects of opioids *JVet Emerg Crit Care*, 20(4): 376–385.

7 Turk, R., Singh, A. and Weese, J. S. (2015) Prospective surgical site infection surveillance. *Dogs Veterinary Surgery*, 44: 2–8.
8 Monibi, F. A., Dodam, J. R., Axiak-Bechtel, S. M., *et al*. (2015) Morphine and buprenorphine do not alter leukocyte cytokine production capacity, early apoptosis, or neutrophil phagocytic function in healthy dogs. *Res in Vet Sci*, 99: 70–76.
9 Quimby, J. M., Smith, M. L. and Lunn, K. F. (2011) Evaluation of the effects of hospital visit stress on physiologic parameters in the cat. *J Feline Med Surg*, 13: 733–737.
10 Bragg, R. F., Bennett, J. S., Cummings, A. and Quimby, J. E. (2015) Evaluation of the effects of hospital visit stress on physiologic variables in dogs. *J Am Vet Med Assoc*, 246: 212–215.
11 Hekman, J. P., Karas, A. Z. and Dreschel, N. A. (2012) Salivary cortisol concentrations and behaviour in a population of healthy dogs hospitalized for elective procedures. *Applied Animal Behavior Science*, 141: 149–157.
12 Calcagni, E. and Elenkov, I. (2006) Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. *Annals of the New York Academy of Sciences*, 1069, 62–76.
13 Molina, P. E. (2005) Neurobiology of the stress response: Contribution of the sympathetic nervous system to the neuroimmune axis in traumatic injury. *Shock*, 24(1): 3–10.
14 Dahl, J. B. and Kehlet, H. (2011) Preventive analgesia. *Curr Opin Anaethesiol*, 24, 331–338.
15 Woolf, C. (2004) Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine*, 140: 441–451.
16 Epstein, M. E., Rodan, I. and Griffenhagen, G. (2015) AAHA/AAFP pain management guidelines for dogs and cats. *J Feline Med Surg.*, 17: 251–272.

Further Reading

Attard, A. R., Corlett, M. J., Kidner, N. J., *et al*. (1992) Safety of early pain relief for acute abdominal pain. *Br Med J*, 305: 554–556.
Mathews, K. A. (ed.) (2017) *Veterinary Emergency & Critical Care Manual*, 3rd edn. LifeLearn, Guelph, Ontario, Canada.

2

Physiology and Pathophysiology of Pain

Tamara Grubb

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. This is useful in that it describes the utility of pain to protect the individual from injury – an appendage placed on something excessively hot causes activation of the pain pathway, the appendage is reflexively withdrawn and tissue damage is prevented, or at least reduced from what it would have been had withdrawal of the appendage not occurred. Although the definition may seem to impart a simple process, the initiation, propagation and subsequent sensation of pain is not at all simple. Pain is a very dynamic and complex phenomenon that involves integration of a variety of receptors, neurotransmitters, neural fibres, neural pathways and both discrete and diffuse anatomic locations. As described, pain can be a normal physiologic response to tissue damage causing withdrawal from a painful stimulus, and as such is called "physiologic" or "protective" pain. Pain can also be an abnormal response causing a situation of intense and/or prolonged pain that is not protective from tissue damage, and as such is called "pathologic" or "maladaptive" pain, among other names (including "clinical pain"). A basic understanding of the pain pathway is important for the appropriate and effective treatment of pain. This understanding will facilitate (1) selection of the most effective analgesic drugs based on the origin of the pain and (2) integration of techniques like multi-modal and preventive (or "preemptive") analgesia to create balanced analgesic protocols.

I. Pain versus Nociception

An understanding of "nociception", versus "pain", is important. *Nociception* describes the physiologic/pathologic process that occurs in mammals, birds, reptiles, amphibians, etc. and likely many other species, in response to a noxious stimulus. The prefix "noci", which means "harm" or "injury", is part of many of the terms describing the process (nociceptive, nociceptor, etc.). *Pain* is defined as a cognitive or emotional response to nociception that occurs in the higher centres of the central nervous system (CNS), such as the cerebral cortex. There are those that believe animals experience only nociception and not pain because they feel that animals do not have the cognitive, and certainly not the emotional, response. However, most animal pain experts, and those of us working with animals, completely disagree with this, especially since animals learn to anticipate and avoid painful situations, which can be indicative of a cognitive response. And as we manage our patients on a daily basis, we certainly recognize the emotional response which is demonstrated in their behaviour (refer to Chapter 8). Pain

Analgesia and Anesthesia for the Ill or Injured Dog and Cat, First Edition. Karol A. Mathews, Melissa Sinclair, Andrea M. Steele and Tamara Grubb.

technically doesn't occur in anesthetized patients since the cognitive or emotional response would be prevented by the anesthetic. However, response to noxious stimuli that occurs under anesthesia is often still described as pain because the noxious surgical stimulus activates the pain pathway and causes the pain-mediated changes described in this chapter. Although the pain centres in the brain don't recognize the pain during anesthesia, it is waiting there for the brain to perceive in recovery.

II. The Pain Pathway in Physiologic Pain

The pain pathway is composed of a series of integrated anatomical structures and physiologic processes that are dynamic and may change their structure or process according to pain source, intensity and/or duration. These changes can be a part of the normal pain response but can also lead to pathologic pain, as discussed in Section III. The processes involved in the pain pathway (Figure 2.1) include transduction, transmission, modulation and perception. Some authors

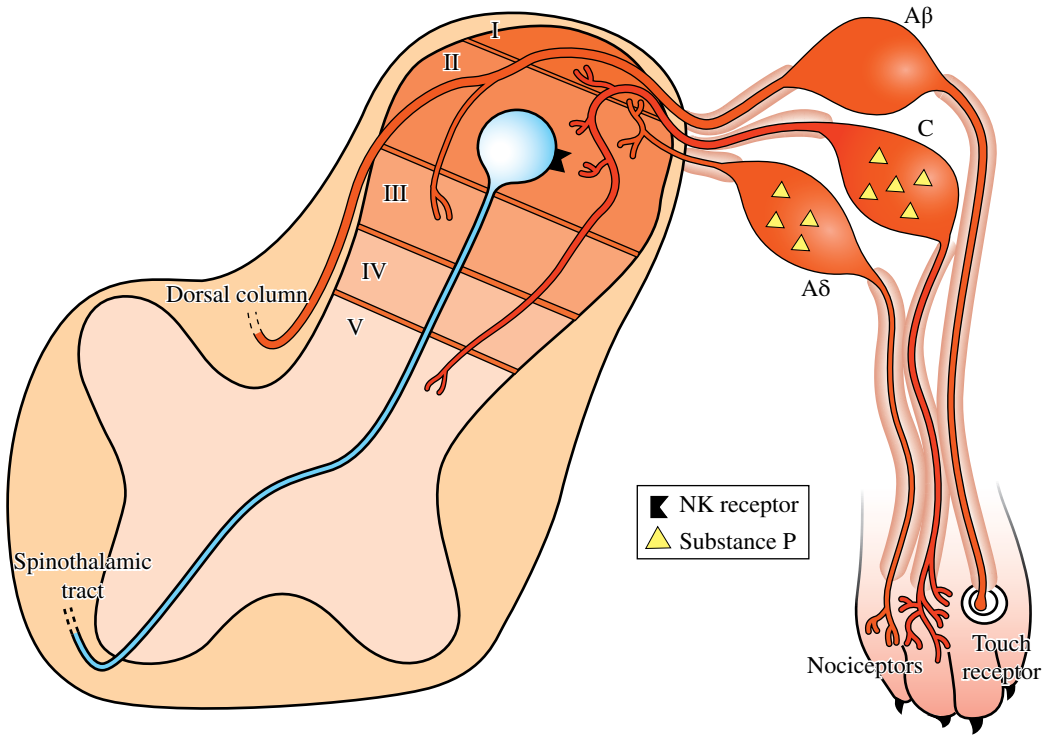

Figure 2.1 Under normal conditions, innocuous sensations or a low-intensity stimulus, such as touch or vibration, is transmitted from the periphery to laminae III and IV of the dorsal horn by means of A-beta fibres; the signal is then relayed to the brain by way of the dorsal column somatosensory pathway. Noxious thermal or mechanical input (transduction), the protective nociceptive "first pain" experience, activates the A-delta fibres, which have small receptive fields, and functions as a warning and is protective to the animal. With increased intensity of the stimulus, C-fibres also conduct impulses along with A-delta fibres. C fibres have a larger receptive field compared with A-delta fibres and are responsible for the "second pain" experience. The A-delta and C fibres enter the dorsal horn of the spinal cord, wherein A-delta fibres almost solely and C fibres predominantly terminate in laminae I and II. The A-delta and C-fibre ganglions express Substance-P (S-P), and the neurokinin-1 (NK1 (S-P)) receptors are expressed in the neurons of lamina II. The signal is then relayed to the brain by way of the spinothalamic tract. *Source:* [9]. Reproduced with permission of Elsevier.

include projection (between modulation and perception) as a separate process. There is also an endogenous analgesic, or "anti-nociceptive", pathway with both ascending and descending components.

A. Transduction

Pain starts when a specialized, high-threshold peripheral sensory receptor, or "nociceptor", is depolarized by a noxious, or "nociceptive", stimulus. The nociceptors are actually not receptors in the traditional sense of the word but are the free nerve endings of A-delta and C nerve fibre dendrites from primary afferent neurons [2]. Most of the nociceptors, especially those from C fibres, are polymodal, meaning that they can be depolarized by a variety of noxious stimuli, including mechanical, thermal and chemical stimuli. For the most part, the nociceptors have no spontaneous depolarization and are high threshold, meaning they respond only to noxious stimuli and not non-noxious stimuli like touch [2]. Depolarization of the nociceptors *transduces* the mechanical information from these stimuli into an electrical impulse. Various ion channels are associated with transduction. These include purinergic, sodium, calcium and potassium channels along with a variety of transient receptor potential (TRP) ion channels. The latter include the transient receptor potential vanilloid (TRPV) receptors that are a major component of pain sensation (especially TRPV1) from heat, cold and chemical stimuli.

The density and exact distribution of nociceptors are species-dependent and often impacted by other factors such as age and disease. In general, they are 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.

B. Transmission

Once the nociceptor has been depolarized, an action potential is *transmitted* to the CNS by the A-delta and C fibre dendrites from their respective nociceptors as described above. Primarily sodium (Na_v 1.1–1.9), but also potassium and calcium, channels are involved in the propagation of the action potential. The Na_v 1.7–1.9 channels seem to be the most important in nociception [3]. A-delta fibres are small myelinated fibres that transmit impulses very rapidly. C fibres are small, unmyelinated and transmit more slowly. Thus, A-delta fibres transmit the "first pain", which is the initial sharp, protective pain, while C fibres transmit the "second pain", which is described as "dull, achy" pain. In addition, impulses transmitted by the A-delta fibres have small receptive fields in the spinal cord, while the receptive fields of impulses carried by C fibres are more diffuse, making pain from A-delta fibres easier to localize than pain from C fibres. The pain impulse passes from both fibres through the first-order neuron in the dorsal root ganglion (DRG) and then to the dorsal horn of the spinal cord, where neurotransmitters (primarily glutamate and S-P) are released.

C. Modulation

The A-delta and C fibres terminate in various lamina in the dorsal horn of the spinal cord (A-delta primarily in lamina I with some in V; C primarily in II), where a variety of scenarios may occur. There is not a direct 1:1 relationship between the number of impulses that enter and those that leave the dorsal horn. The impulses may be sent directly to the brain without change or may be *modulated* (amplified or inhibited) by interneurons or descending projections. They can bifurcate, sending branches that ascend or descend several spinal cord segments (Lissauer's tracts) before synapsing. In the simplest process, the signal from the first-order neuron causes

a release of an excitatory amino acid (primarily glutamate but also aspartate) and/or a neuropeptide (S-P or neurokinin) which crosses the neuronal synapse to activate the second-order neuron in the dorsal horn, which is most likely to be an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or a kainate (KAI) receptor.

Once the second-order, or "projection", neuron, is activated, the signal travels to the contralateral side of the dorsal horn and is transmitted (or "projected") up an ascending (or "projecting") tract. The ascending tracts are species-specific (and not well described in all species) as to their presence, location and importance. The tracts primarily include the spinothalamic (STT), spinocervicothalamic (SCT), spinoreticular (SRT) and spinomesencephalic tracts (SMT), with the STT and SCT likely playing the most prominent roles in most mammals [4].

D. Perception

There is no specific pain centre in the brain, and nociceptive impulses from the ascending tracts may arrive primarily at the thalamus, hypothalamus and structures of the midbrain. At these locations, the second-order neurons synapse and the impulses are transmitted to various cortical and subcortical regions, including the somatosensory cortex, periaqueductal gray (PAG) region, reticular formation and the limbic system. This diverse pattern of distribution results in a variety of outcomes, which include pain perception, but also initiation of descending facilitatory (which increase pain) and inhibitory (which decrease pain) processes, wakefulness, behavioural reactions, emotional changes (at least in humans), etc. A third-order neuron transmits the impulse from the thalamus to the somatosensory cortex where the pain signal is "perceived" and identified by location, type and intensity. For intensity, depolarization of neurons is either "all" or "none" so varied pain intensity does not result from different stimulus strength but rather from the number of stimuli. Perception and interpretation of the impulse in the somatosensory cortex initiates a behavioural response, which can manifest itself in a number of ways, including withdrawal from, or aggression towards, the source of the pain. Impulses at the reticular system activate autonomic and motor responses, and impulses at the limbic system are responsible for emotional responses (at least in humans).

E. Endogenous Analgesic Pathways

1. Descending Inhibitory Pathway

Descending inhibition of ascending afferent pain impulses can be activated in various sites, including the cortex, thalamus, midbrain, brainstem and dorsal horn of the spinal cord. The inhibitory process is primarily controlled by the PAG, which appears to be a "coordinating centre" for the endogenous analgesic system. The main effective site of the descending pathway is the dorsal horn of the spinal cord, where a descending projection neuron from the PAG will synapse in the gap between the axon of the sensory first-order neuron and the second-order neuron, releasing neurotransmitters, including endogenous opioids (endorphins, enkephalins, dynorphins), serotonin (5-HT), norepinephrine, gamma-aminobutyric acid (GABA) and glycine. This alleviates propagation of the pain impulse at the synapse by release of inhibitory neurotransmitters that bind to both presynaptic and postsynaptic sites. Presynaptic binding causes decreased release of excitatory neurotransmitters into the synapse, and postsynaptic binding causes decreased propagation of the pain stimulus on the second-order neuron. The endogenous system is likely most effective in alleviating mild pain and can provide a brief period of relief for moderate to severe acute pain during high-stress states (like survival situations).

2. Ascending Analgesic Pathway

A-beta receptors and fibres, which travel with the A-delta and C nociceptors and fibres, are myelinated and have a rapid conduction velocity. These generally conduct non-noxious (non-nociceptive) stimuli such as touch and movement and can also recruit inhibitory neurons in the dorsal horn of the spinal cord (gate control). This appears to be part of the explanation for why rubbing a painful site may actually decrease the level of pain. Wide dynamic range (WDR) receptors or neurons may also initiate inhibitor responses to pain in the dorsal horn of the spinal cord. These neurons receive input from A-beta, A-delta and C fibres and respond to all forms of input, from light touch to noxious stimuli, in a graded fashion depending on stimulus intensity. The WDR output from normal A-beta activation is likely inhibitory.

III. The Pain Pathway in Pathologic Pain

With tissue injury, pain does not end with recognition of pain in the cortex and removal of the body part from the noxious stimuli. Ongoing mild to moderate pain from tissue that is currently injured is not necessarily "pathologic" – it can still be "protective" – but pain that is more intense than necessary for protection, and pain that continues after the injury has healed, is indeed pathologic pain. If pain is not necessary for protection, it serves no biologic purpose and results in needless decreased quality of life for the patient. Pathologic changes that occur in the pain pathway include peripheral sensitization, recruitment of fibres that normally don't carry noxious stimuli (A-beta fibres), central sensitization and dysfunction of the descending inhibitory pathway. These changes can cause more significant conditions, including hyperalgesia and/or allodynia. Hyperalgesia is an exaggerated pain sensation to a normally low-level pain stimulus and allodynia is a pain sensation from a normally non-painful stimulus, such as light touch. These changes may become permanent, or at least long-lasting, causing chronic pain states, which are often difficult to treat with standard analgesic therapy. An even more sinister type of pain, neuropathic pain, can be caused or enhanced by these changes.

To prevent or reduce pathologic pain, early administration of appropriate analgesics and careful surgical technique and tissue handling are essential. In addition, **multi-modal analgesia**, meaning utilization of more than one drug class and/or analgesic technique [5], is more likely to prevent the development of pathologic pain and is almost always required to treat pathologic pain once it has occurred because of the complexity of the pain pathway and the variety of changes that occur with the onset and progression of pathologic pain. There is no single therapy that can treat the myriad pathway alterations. The discussion below includes a description of pain pathway changes induced by pathologic pain and a list of drugs or compounds that affect the pain pathway at each step. The lists are by no means exhaustive.

A. Transduction

With tissue injury, damaged structural cells and damaged, and recruited, inflammatory cells (e.g. neutrophils, mast cells, macrophages and lymphocytes) release a variety of intracellular compounds that accumulate in the area of the injury which expands as cells on the periphery of the original injury site are also damaged, enlarging the painful area. Such a very large variety of compounds can be involved (e.g. H+, K+, prostaglandins, interleukins, tumour necrosis factor, bradykinin and S-P) that this group of compounds is often called the "sensitizing soup". The result is continued tissue damage as the "soup" expands and causes injury to adjacent cells, creating an ever-widening area of damage, recruitment of more A-delta and C nociceptors, and activation of the arachidonic acid pathway and inflammation. In addition, the "soup" causes a reduced depolarization threshold of nociceptors, which decreases the

level of stimulus needed to activate A-delta and C nociceptors; induces changes in A-beta nociceptors, which makes them responsive to noxious stimuli (these normally only transduce touch and other non-noxious stimuli); and causes activation of "silent nociceptors" (likely C nociceptors) that were not participating in the pain transduced from the original injury. These processes create *peripheral sensitization*, which is a major component of hyperalgesia and also contributes to allodynia.

Example drugs or compounds effective at this site: non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, capsaicin.

B. Transmission

With the recruitment of additional A-delta and C fibres and transformation of A-beta fibres to transmit noxious stimuli, the number and frequency of nociceptive impulses transmitted to the dorsal horn of the spinal cord are increased, thus amplifying the pain signal. Na + channels (especially Na_v 1.8) can become hyperexcitable and exhibit spontaneous electrical activity or pathological electrical activity [3].

Example drugs or compounds effective at this site: local anesthetics, opioids, alpha$_2$ agonists, tetrodotoxin.

C. Modulation

The processes that occur at the spinal cord in pathologic pain are numerous and complex. These processes can contribute to allodynia and central sensitization, and include (but are not limited to):

- The increased frequency and intensity of pain impulses reaching the dorsal horn (i.e. increased "afferent traffic") activate not only the AMPA and KAI receptors but also the N-methyl-D-aspartate (NMDA) receptors, which are normally dormant. Activation of the NMDA receptors, which is integral to the process of central sensitization, occurs secondary to "flooding" of the second-order synapse with excitatory neurotransmitters from the increased afferent input and from additional input from WDRs.
- As stated, the WDR neurons receive input from A-beta, A-delta and C fibres and respond to all forms of input (from light touch to noxious stimuli) in a graded fashion depending on stimulus intensity. Repetitive firing of A-beta and C fibres causes a noxious stimulus at the WDR.
- Central activation of the arachidonic acid pathway occurs with repetitive noxious stimuli, which may also influence NMDA-receptor activation and activity along with contributing to centrally mediated hyperalgesia.
- Non-neuronal cell types, such as astrocytes and microglia, that normally do not play a role in pain transmission can be activated or altered and can enhance pain transmission with repetitive stimuli [6].
- A-beta fibres can sprout into lamina 1 of the spinal cord and activate neurokinin (NK)-1 receptors.
- Nerve injury may also disrupt the A-beta-fibre-mediated inhibition and the GABA-mediated inhibition of pain transmission neurons in the dorsal horn [7–9]. The loss of this activity may be within interneurons, which ultimately releases the "brake" on central sensitization of dorsal horn neurons. The loss of this inhibitory process may contribute to spontaneous pain, hyperalgesia or allodynia following nerve injury [7–9].

Example drugs or compounds effective at this site: opioids, NMDA-receptor antagonists (ketamine, amantadine), alpha$_2$ agonists, local anesthetics, gabapentin, NE and 5-HT uptake inhibitors, tricyclic antidepressants, NSAIDs.

D. Perception

Previous pain experiences, agitation, fear, sensory triggers (smells, sounds, etc.), sensory distractors (smells, music, presence of a loved one, etc.), culture, social status, sleep deprivation and myriad other things can alter the perception of pain – at least in humans. It would appear that, at the very least, previous pain experiences may impact perception in animals because they do develop avoidance responses to repetitive noxious stimuli, which could be interpreted as a cognitive learned response. A curious phenomenon that occurs in humans, but is not yet reported in animals, is loss of cerebral gray matter in chronic pain states [10]. Whether this is caused by the pain itself or is an attempt to reduce the magnitude of the perception of pain is unknown.

Example drugs or compounds effective at this site: opioids, alpha$_2$ agonists, some general anesthetic drugs, NMDA-receptor antagonists, tricyclic antidepressants, NE and 5-HT uptake inhibitors.

E. Descending Inhibitory Pathway

Decreased efficacy of the descending inhibitory limb of the pain pathway may play a large role in the initiation, maintenance and degree of pathologic pain [11]. Reduced opioid receptor function with subsequent reduced response to IV or intrathecal opioids, altered or reduced levels of endogenous norepinephrine and serotonin activity at the spinal and supraspinal levels, and disruption of A-beta-mediated inhibition all contribute to the abnormal response of the descending inhibitory limb [9]. The loss of this inhibitory process, which serves as the "brake" in the pain pathway, may contribute to spontaneous pain, hyperalgesia and/or allodynia [7–9].

Example drugs or compounds effective at this site: Endogenous opioids, serotonin and norepinephrine reuptake inhibitors affect this portion of the pathway, as do drugs that increase the inhibitory neurotransmitter GABA and cannabinoids.

IV. Specific Types of Pain

A. Neonatal/Pediatric Pain

In both humans and animals, neonates and pediatric patients do feel pain. Untreated pain in neonates can cause amplified pain sensation as the patient ages and may lead to chronic pain in adulthood (refer to Chapter 25).

B. Neuropathic Pain

Various studies have identified the decreased efficacy of the descending inhibitory pathways in animals with neuropathic lesions and have demonstrated reduced opioid receptor function [13, 14]. Because descending inhibition normally acts as a spinal "gate" for sensory information, reduced inhibition increases the likelihood that the dorsal horn neuron will fire spontaneously or more energetically to primary afferent input [15]. While opioid receptors are less responsive in neuropathic pain, it appears that descending noradrenergic inhibition, and increased sensitivity of spinal neurons to alpha$_2$ agonists, may occur with peripheral inflammation and nerve injury [15]. Refer to Chapter 3 for a detailed discussion.

C. Visceral Pain

The physiology/pathophysiology of visceral pain is very complex and comprises afferent and efferent innervations, autonomic nervous system modulation, and central processing.

Peripheral and central sensitization may occur [16, 17]. Refer to Chapter 4 for details, as the understanding of these processes is important in managing the specific visceral pain experienced within the thorax, abdomen and pelvis.

D. Breakthrough Pain

Breakthrough pain (BTP) is described as an abrupt, short-lived and intense pain that "breaks through" the around-the-clock analgesia that controls persistent pain [18, 19]. This may occur in the post-operative setting or intermittently at home in animals on chronic pain medication for cancer or neuropathic pain. If a single analgesic agent is being used, consider the addition of other analgesics of a different class (refer to Chapter 6 and information contained in scenarios throughout this book). When BTP occurs at home, a careful history is required to obtain clues about the cause and pattern of BTP. It may be difficult to administer oral medication when animals exhibit excruciating pain. If this cannot be controlled, parenteral or transdermal administration has to be considered in addition to oral medication. The dose and/or dosing frequency of the around-the-clock analgesic should be adjusted for patients with end-of-dose BTP. In addition to pharmacologic therapy, non-pharmacologic strategies are often helpful in alleviating pain and anxiety. (refer to Chapter 15).

E. Stimulus-Evoked/Movement-Evoked Pain

As the name suggests, stimulus-evoked/movement-evoked pain does not occur when the patient is resting quietly with no movement or touch. While managing pain in situations other than when the patient is at rest can be challenging, this pain should not be ignored by preventing movement, as movement is essential for a normal recovery. Consider analgesic protocols and procedures specifically prepared for the individual patient and their associated pain stimulus (refer to Chapter 6). An example of stimulus-evoked pain is pressing around the surgical wound to assess the presence/degree of mechanical hyperalgesia. The response and extent of the anatomical area eliciting pain will indicate the degree of pain and solicit a review of the analgesic protocol.

References

1 Merskey, H. and Bogduk, N. (1994) *Classification of Chronic Pain: Descriptions of chronic pain syndromes and definitions of pain terms*. IASP Press, Seattle.
2 Woolf, C. J. and Ma, Q. (2007) Nociceptors: Noxious stimulus detectors. *Neuron*, 55(3): 353–364.
3 Levinson, S. R., Luo, S. and Henry, M. A. (2012) The role of sodium channels in chronic pain. *Muscle Nerve*, 46(2): 155–165.
4 Kajander, K. C. and Giesler, G. J., Jr (1987) Effects of repeated noxious thermal stimuli on the responses of neurons in the lateral cervical nucleus of cats: Evidence for an input from A-nociceptors to the spinocervicothalamic pathway. *Brain Res*, 436(2): 390–395.
5 Lamont, L. A. (2008) Multimodal pain management in veterinary medicine: The physiologic basis of pharmacologic therapies. *Vet Clin North Am Small Anim Pract*, 38(6): 1173–1186.
6 D'Mello, R. and Dickenson, A. H. (2008) Spinal cord mechanisms of pain. *Br J Anaesth*, 101(1): 8–16.
7 Taylor, B. K. (2001) Pathophysiologic mechanisms of neuropathic pain. *Curr Pain Headache Rep*, 5: 151–161.

8 Woolf, C. J. (2004) Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy. *Life Sciences*, 74: 2605–2610.
9 Mathews, K. A. (2008) Neuropathic pain in dogs and cats: If only they could tell us if they hurt. *Vet Clin North Am Small Anim Pract*, 38(6): 1365–1414.
10 Apkarian, A. V., Sosa, Y., Sonty, S., *et al.* (2004) Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci*, 24(46): 10410–10415.
11 Ren, J. and Ruda, R. (2002) Descending modulation in persistent pain: An update. *Pain*, 100(1–2): 1–6.
12 Cui, M., Honore, P., Zhong, C., *et al.* (2006) TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. *J Neurosci*, 26(37): 9385–9393.
13 Zimmerman, M. (2001) Pathobiology of neuropathic pain. *Eur J Pharmacol*, 429: 23–37.
14 Mayer, D. J., Mao, J. and Price, D. D. (1995) The development of morphine tolerance and dependence is associated with translocation of protein kinase C. *Pain*, 61: 365–374.
15 Tanabe, M., Takasu, K., Kasuya, N., *et al.* (2005) Role of descending noradrenergic system and spinal alpha$_2$-adrenergic receptors in the effects of gabapentin on thermal and mechanical nociception after partial nerve injury in the mouse. *Br J Pharmacol*, 144: 703–714.
16 Joshi, S. K. and Gebhart, G. F. (2000) Visceral pain. *Current Review of Pain*, 4(6): 499–506.
17 Knowles, C. H. and Aziz, Q. (2009) Basic and clinical aspects of gastrointestinal pain review. *Pain*, 141: 191–209.
18 Payne, R. (2007) Recognition and diagnosis of breakthrough pain. *Pain Med*, 8(suppl. 1): S3–S7.
19 McCarberg, B. H. (2007) The treatment of breakthrough pain. *Pain Med*, 8(suppl. 1): S8–S3.

Further Reading

Shilo, Y. and Pascoe, P. J. (2014) Anatomy, physiology and pathophysiology of pain. In: Egger, C. M., Love, L. and Doherty, T. (eds), *Pain Management in Veterinary Practice*. Wiley-Blackwell, Oxford: 9–29.

3

Physiologic and Pharmacologic Applications to Manage Neuropathic Pain

Karol Mathews

Neuropathic pain is re-defined by the International Association for the Study of Pain (IASP) as pain caused by a lesion or disease of the somatosensory nervous system and may be generated by either the peripheral or central nervous system, or both [1]. A very broad term is "neurogenic pain". There follows a plethora of changes in the peripheral nervous system (PNS), spinal cord, brainstem and brain as damaged nerves fire spontaneously and develop hyper-responsivity to both inflammatory and normally innocuous stimuli [1]. Refer to Chapter 2 for details on the anatomy and physiology of pain transmission in general.

Neuropathic pain is frequently associated with chronic pain. However, it also occurs in the acute setting either pre-operatively, when associated with trauma, or a neoplastic or inflammatory condition encroaching on neural tissue, or post-operatively, where transient or persistent iatrogenic injury has occurred. Patients noted to be at risk of progression to persistent pain include those with severe pain and those with injury to any part of the peripheral or central nervous system (CNS). The importance of being aware of the animals "at risk" of development of chronic neuropathic pain in the acute setting is to ensure that appropriate intervention is instituted pre-, intra- and post-operatively, and practising meticulous surgical technique to prevent such a debilitating situation, which may be difficult to diagnose once established at a later date.

In the chronic setting, the clinical signs have been insidious and present for weeks to several months with an obvious lesion being difficult to find. As pain in general can be difficult to recognize and isolate in many veterinary patients, neuropathic pain can be extremely difficult to identify unless we appreciate the occult nature of many of the predisposing causes. Frequently, neuropathic pain induces a response which may be interpreted as a primary behavioural problem and may, therefore, go untreated. Two major events occur in the development of chronic neuropathic pain: (1) abnormal peripheral input and (2) abnormal central processing. The situations where pain may be a cause for behavioural changes are:

- in the acute pain setting (at home or in the hospital);
- at a later period following a traumatic or surgical; experience
- due to a chronic primary lesion affecting the:
  - somatosensory and visceral peripheral nerve(s),
  - the meninges, vertebral column, spinal cord and its nerve roots, or
  - a lesion in the brain.

Analgesia and Anesthesia for the Ill or Injured Dog and Cat, First Edition. Karol A. Mathews, Melissa Sinclair, Andrea M. Steele and Tamara Grubb.

I. Physiology of Neuropathic Pain

The origin of neuropathic pain may be difficult to diagnose unless an obvious predisposing lesion or injury to the nervous system is easily identified, or a genetic predisposition exists. Understanding the physiology and events that occur in the nervous system, originating from poorly managed acute pain, chronic pain or from primary lesions within the nervous system is important, as individual mechanisms causing pain are targets for therapeutic consideration. Some lesions may be amenable to surgical therapy, whereas others will require specific pharmacological intervention.

A. The Patient's Experience

Enhanced sensation at a certain level of tactile stimulus in areas normally hypoesthetic at rest [2, 3], for example:

- paresthesias (tingling, prickling, burning);
- hyperesthesias (heightened sensation to a nociceptive stimulus); and
- dysesthesias (unpleasant or painful sensation).

With these experiences the spontaneous actions of a dog or cat, in response to these sensations, can easily be interpreted as behavioural by the owner.

B. The Quality and Pattern of Altered Sensitivity

The quality and pattern of altered sensitivity in neuropathic pain differs from transient or inflammatory pain. As examples:

A cold stimulus or warm stimulus, such as applying a cold or warm pack to an acutely injured joint or muscle to reduce the inflammatory pain in the "normal" or "naive" painful individual, would result in an excruciating painful experience in a patient with neuropathic pain [2]. This difference in "experience" is due to a reorganization of sensory transmissions within the nervous system which occur following nerve injury. These comprise alterations in expression of neurotransmitters, neuromodulators, receptors, ion-channels, especially the tetrodotoxin-resistant (TTR-X) sodium channels [4], and structural proteins. Some of these changes are involved in the reparative process but others contribute to neuropathic pain. Examples of neural response to injury include:

1. The A-beta (touch) fibres may sprout into the laminae II region of the dorsal horn, the same area as central terminals of C fibres (nociception), where Substance-P (S-P) and its receptors (neurokinin-1(NK_1)) are expressed [2] (Figure 3.1).
2. Due to nerve injury, the disruption of the glial ensheathment allows the adjacent denuded axons of A-beta fibres and C fibres to make contact facilitating both electrical (aphaptic) and chemical (via diffusible substances) cross-excitation [5]. A cross-after-discharge can also occur whereby normal A-beta fibres can activate C fibres [2, 5]. This occurs when light, innocuous stimuli are applied to the area subserved by the nerve-injured area, and the stimuli transmitted by the A-beta fibres are processed in the dorsal horn as C fibre sensory afferent stimuli with subsequent pain transmission [2] (see Figure 3.1).
3. During the healing process, there may also be a connection between the A-beta fibres and the C fibres. Therefore, the transmission of a normal innocuous "touch" stimulus elicited during transduction of the A-beta fibres is coupled to the axon of the C fibre. Subsequent transmission is then via the C fibre, where it is interpreted centrally as a noxious stimulus (allodynia) [2] (see Figure 3.1).