The Veterinary Journal 230 (2017) 52–61

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Chronic maladaptive pain in cats: A review of current and future drug treatment options

Derek Adrian[a], Mark Papich[b], Ron Baynes[c], Jo Murrell[d], B. Duncan X. Lascelles[a,e,f,*]

[a] Comparative Pain Research and Education Centre, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
[b] Molecular and Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
[c] Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
[d] School of Veterinary Sciences, University of Bristol, Bristol, UK
[e] Center for Pain Research and Innovation, UNC School of Dentistry, Chapel Hill, NC, USA
[f] Center for Translational Pain Research, Department of Anesthesiology, Duke University, Durham, NC, USA

ARTICLE INFO

Keywords:
Maladaptive pain
Cats
Analgesia
Central plasticity
Chronic pain

ABSTRACT

Despite our increasing understanding of the pathophysiology underlying chronic or maladaptive pain, there is a significant gap in our ability to diagnose and treat the condition in domestic cats. Newer techniques being used to identify abnormalities in pain processing in the cat include validated owner questionnaires, measurement of movement and activity, and measurement of sensory thresholds and somatomotor responses. While some data are available evaluating possible therapeutics for the treatment of chronic pain in the cat, most data are limited to normal cats. This review details our current understanding of chronic or maladaptive pain, techniques for the detection and measurement of the condition and the associated central nervous changes, as well as an overview of the data evaluating potential therapeutics in cats.

Introduction

While cats have become a very popular pet worldwide- with an estimated 75+ million in the US alone, the assessment and treatment of pain in cats has lagged behind that of dogs (Robertson, 2008b). Though this knowledge gap is diminishing, most information on pain control in cats exists regarding peri-operative analgesic use, (Brondani et al., 2011; Johnson, 2013; Calvo et al., 2014; Epstein et al., 2015) with chronic pain conditions still being undiagnosed and under-treated (Robertson, 2008b; Lascelles and Robertson, 2010; Lorena et al., 2013). Chronic pain situations typically do not have easily identifiable inciting incidents and the behavioral changes develop slowly and are often subtle. This makes measurement of chronic or long-standing pain conditions difficult, and although recent progress has been made in the development of tools to assess chronic pain (Zamprogno et al., 2010; Benito et al., 2012; Benito et al., 2013; Gruen et al., 2015) our ability to measure chronic pain lags behind that of acute pain in veterinary species. The relative lack of validated methods of chronic pain assessment contributes to our inability to assess efficacy of analgesics for the alleviation of such pain in cats. This review details our current understanding of chronic or maladaptive pain, techniques for the detection and measurement of the condition and the associated central nervous changes, as well as an overview of the data evaluating potential therapeutics in the cat.

The literature review was performed by searching on several databases, including PubMed, CAB Abstracts, and Google Scholar. Specific search for medications of interest were based on: personal experience, use, or knowledge, anecdotal reports of use or efficacy, recommendations and guidelines for the treatment of pain in cats, medications being currently researched, etc. Keywords used included: pain; chronic pain; maladaptive pain; feline; feline pain; osteoarthritis; degenerative joint disease; analgesics; pharmacokinetics; efficacy; etc.

Chronic maladaptive pain

Chronic pain has been defined in human medicine as any pain that lasts more than 3–6 months (Merskey and Bogduk, 1986), but the relevance of this timeline to veterinary species with

* Corresponding author at: Comparative Pain Research and Education Centre, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA.
E-mail addresses: duncan_lascelles@ncsu.edu, bdxlascelles@gmail.com (B. D.X. Lascelles).

http://dx.doi.org/10.1016/j.tvjl.2017.08.006
1090-0233/

considerably shorter lifespans should also be considered. Different disease conditions like cancer may also affect the timeline, as it may not be prudent to 'delay' treatment, or pathologies where the normal healing and recovery period is expected to be much shorter. This difficulty in clearly demarcating the transition from acute to chronic pain has led to a growing realization that previously termed acute and chronic pain are actually on a continuum, and alternative definitions may be more useful in the context of understanding pain and how to treat it (Woolf, 2010). Recently, the terms 'adaptive' and 'maladaptive' have been suggested as terms that better describe pain (Figs. 1 and 2). Adaptive pain encompasses both nociceptive and inflammatory pain (Woolf, 2010). Nociceptive pain is only activated by high-threshold noxious stimuli, including stimuli that cause tissue injury. Inflammatory pain occurs after tissue damage and produces heightened sensitivity of the tissue associated with a classical inflammatory response. Both of these types of pain are considered protective, or 'adaptive' pain in that they serve to sense and/or avoid actual or potential tissue damage. These typically have an easily identifiable cause (surgery, injury, etc.), and are reversible. Maladaptive pain, on the other hand, is not protective, and is primarily due to plastic changes in the pain processing system. It can be further divided into neuropathic pain, which is pain resulting from direct damage to neural tissue, and functional pain, where there are no neural lesions or inflammation, and pain is driven by dysfunction or malfunction of the nociceptive system. Classically, neuropathic pain is thought of as resulting from gross, obvious damage to the spinal cord, or obvious damage to peripheral nerves such as with peripheral nerve sheath tumors or surgical trauma. However, increasingly it is recognized that many diseases, such as osteoarthritis (OA) and cancers, may involve a degree of peripheral neuropathy via either direct damage to nerve endings present in the tissues, or via increased innervation that accompanies joint remodeling and angiogenesis (Ivanavicius et al., 2007; Im et al., 2010; Bennett et al., 2012; French et al., 2017). This explains the neuropathic pain-like symptoms reported in many human patients with OA. Similarly, the obvious example of functional pain is phantom limb pain or fibromyalgia — there is no evidence of a peripheral lesion or inflammation, yet there is increased sensitivity to stimuli and spontaneous pain. Yet increasingly, it is recognized that many conditions, such as OA, have a component of functional pain — changes in the central nervous system function that heightens sensitivity or results in spontaneous pain. It has been previously suggested that there is a central or maladaptive drive to pain in a significant portion (20–40%) of human patients suffering from osteoarthritis-associated

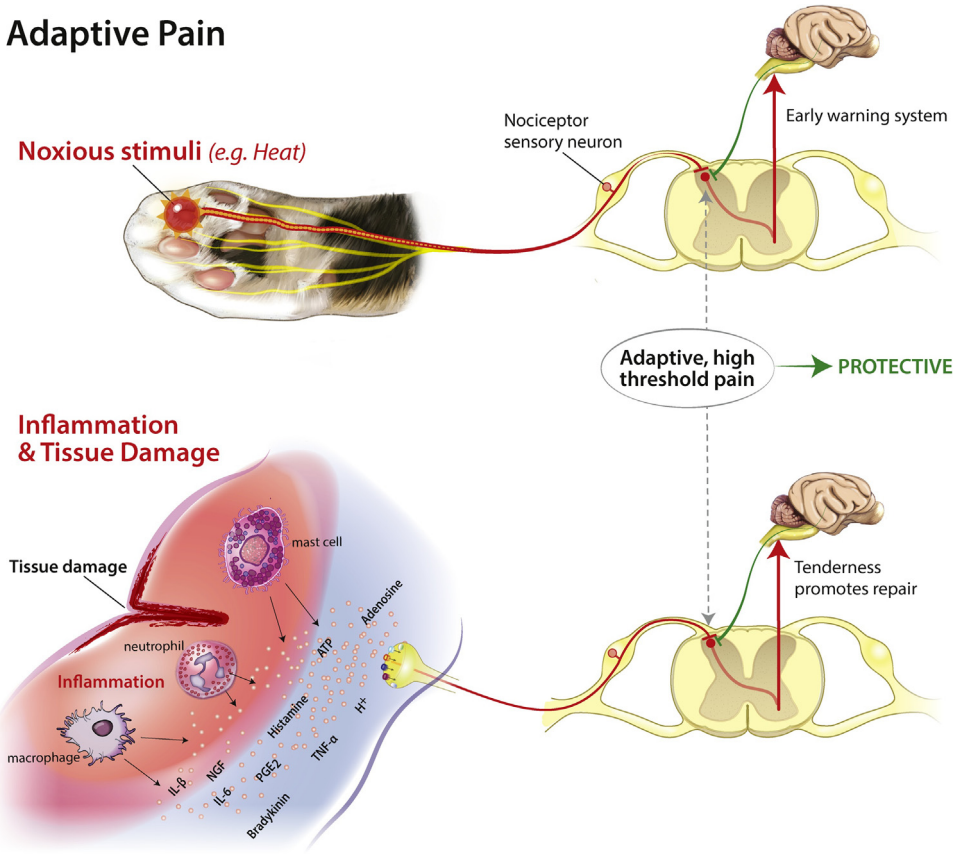

Fig. 1. Schematic illustration of adaptive pain. Nociceptive pain — a noxious stimulus (red starburst) activates high-threshold nociceptive primary afferent sensory neurons (red/yellow line) with cell bodies in the dorsal root ganglion (DRG), and termination in the dorsal horn (DH). Here, the afferent signal is transmitted to the second order neuron via mono- or multi-synaptic processes, and crosses over to the other side of the spinal cord, then transmitted to the brain via ascending tracts in the spinal cord (red arrow), where it is interpreted as a warning of actual or potential tissue damage. There is tonically active descending inhibition (green line) from the CNS (channeled via the rostro-ventromedulla) that helps control whether the information from the primary afferent neuron is blocked at the level of entry into the DH of the spinal cord. Inflammatory pain — local tissue damage results in release of inflammatory mediators, recruitment of inflammatory cells and further release of inflammatory mediators. These mediators either sensitize sensory nerves, or directly stimulate them, resulting in a lowering of thresholds in sensory nerves and generation of action potentials (nociceptive signals). These signals are carried by afferent neurons (red line) with cell bodies in the DRG and terminals in the DH. As before, ascending fibers carry the nociceptive input to the brain along ascending tracts (red arrow), and descending inhibitory signals (green line) may dampen down the input at the level of the spinal cord. The increased sensitivity in the periphery associated with inflammatory pain following tissue damage promotes protection of the area, allowing it to heal.