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Review

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

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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.

Keywords: Maladaptive pain; Cats; Analgesia; Central plasticity; Chronic pain

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 don't 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 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 pain (Crawford et al., 1998; Ivanavicius et al., 2007). This underscores the importance of understanding the driving factors of a patient's pain, as one patient may suffer from multiple types.

Central to the concept of maladaptive pain is the phenomenon of central plasticity (also referred to as central sensitization), initiated through cellular wind up (Woolf, 2011). While wind-up is a neuron's increasing response/output resulting from repeated, identical stimuli, central plasticity is the global response that lasts autonomously after the conditioning (original) stimulus has been discontinued, or is sustained with low level nociceptor input from the

periphery (Woolf, 2011). This results in a stronger painful reaction to a less intense (hyperalgesia) or previously innocuous stimulus (allodynia), and increases in the receptive fields of neurons, or the region of tissue that a neuron functionally innervates and responds to stimuli in. Central plasticity is driven by changes at various levels of the sensory transmission axis – primary afferent fiber, spinal cord and higher centers. In general, the processes driving central plasticity are a combination of increased neuronal excitability, facilitated synaptic transmission and decreased inhibitory influences (Woolf, 2011). However, as well as a gain in function, some processes are down-regulated (loss of gain) and so the term central plasticity is preferred over central sensitization.

Clinical long-standing pain (chronic pain) is a complex mixture of adaptive (inflammatory) and maladaptive (neuropathic, functional) pain. It is likely that different neurobiological processes are responsible for the different components of long-standing pain, but it is also likely that there is tremendous overlap. Most information about the processes involved in the maladaptive component of long-standing pain have been derived from work in rodents, using models of neuropathic pain. A multitude of mechanisms play varying roles in maladaptive pain states, and a laudable clinical goal would be to be able to understand the mechanisms responsible for pain in an individual, and so make informed choices about analgesics. Currently it is impossible to predict the mechanisms responsible for the pain state in individual patients, however, progress is being made in this area, with recent studies in humans testing the function of the endogenous analgesic mechanisms to predict response to analgesics (Yarnitsky 2012; Edwards 2016).

Most chronic diseases that are associated with pain consist of several different pain components, including both an active, sustained inflammatory component (as in degenerative joint disease, gingivostomatitis, and others) as well as the maladaptive pain with associated neuronal changes and sensitization (Lee et al., 2011; Woolf, 2011; Baron et al., 2013). Although is it not easy to clinically recognize inflammatory versus maladaptive pain states, there is increasing recognition that many common long-standing diseases are associated with central plasticity, and so maladaptive pain. Indeed, it was recently shown that dogs with OA have measureable central sensitization indicative of maladaptive pain (Knazovicky et al., 2016). Commonly occurring diseases that are possibly associated with a component of maladaptive pain in the cat include osteoarthritis and degenerative joint disease, interstitial cystitis, gingivostomatitis, diabetic neuropathy, cancers, ocular pathology (including glaucoma, chronic anterior uveitis), dermatological conditions (including chronic infections, burns, slow-healing wounds, secondary effects of radiation therapy), and others (Robertson and Lascelles, 2010).

It is important to clarify that chronic pain can exist on a continuum, and can in fact be comprised of multiple driving mechanisms. In some chronically painful conditions, the driving condition may start and remain as inflammatory pain, with an easily understood coupling of peripheral disease with degree of pain. In these painful conditions, nonsteroidal anti-inflammatory drugs (NSAIDs) are expected to be effective. However, it is likely that in many cases, the ongoing nociceptive input into the nervous system, along with damage to nerve endings as a result of the peripheral disease process can cause changes in the central nervous system and therefore produce maladaptive pain. It is this maladaptive component that makes chronic pain difficult to treat. Hence the search for novel, non-NSAID therapies that can be used

along with, or in place of, NSAIDs. At this moment, we are limited in that we cannot clinically differentiate between maladaptive pain, and pain with a purely inflammatory drive.

Assessment of chronic pain in cats

Recently, progress has been made in the assessment of chronic pain in the cat using owner questionnaires, called Clinical Metrology Instruments (CMIs). The two most studied CMIs are the Client Specific Outcome Measures (CSOM) and Feline Musculoskeletal Pain Index (FMPI; Gingerich and Strobel, 2003; Lascelles et al., 2007; Lascelles et al., 2008; Lascelles et al., 2010; Benito et al., 2013; Gruen et al., 2015).

The objective measurement of movement or activity also have been developed as methods to assess the impact of chronic/maladaptive pain and its treatment. Recently, activity monitors that record changes in acceleration associated with movement have been used as an objective outcome measure of mobility in cats (Lascelles et al., 2010; Guillot et al., 2012; Gruen et al., 2014). Cats are fitted with a small accelerometer on a collar or harness, and allowed to move about normally in their home environment. This the tool can discriminate between normal and affected research cats (Guillot et al., 2012), and can even be used to show treatment effects in client-owned affected cats (Lascelles et al., 2007; Lascelles et al., 2010; Guillot et al., 2013; Gruen et al., 2014; Gruen et al., 2016).

To understand the mal-function of the somatosensory system present with maladaptive pain, methods evaluating sensorimotor function are needed. Quantitative sensory testing (QST) involves the measurement of the stimulus (mechanical, thermal hot/cold, etc.) strength or

frequency of application required to elicit a withdrawal or response (e.g. head turn, limb withdrawal) by the patient, with the end of the test usually determined by observation of the response. It is useful for semi-objectively assessing changes in sensation, especially in relation to central plasticity, and its associated allodynia, hyperalgesia, enhanced temporal summation (an increasing response to repetitive stimuli), etc. (Guillot et al., 2014). While QST is in its early development in cats, it can discriminate between healthy, non-affected cats, and those with OA (Guillot et al., 2014). Other methods such as the measurement of Nociceptive Withdrawal Reflexes (NWR) have been explored in dogs, but not yet in cats (Bergadano et al., 2006; Hunt et al., 2016). NWR Testing measures the magnitude of the withdrawal responses to various stimuli using EMG. This modality can evaluate the threshold to elicit withdrawal, in addition to the effect on withdrawal latency and magnitude after delivering repeated stimuli (temporal summation). Data produced are objective, as opposed to the semi-objective QST methodology. NWR testing is proposed to measure central plasticity and associated changes in pain processing, and affected patients are expected to have lower thresholds and higher or stronger EMG responses.

Overall, our ability to accurately measure chronic pain is limited, and our ability to measure the maladaptive component of this pain is even more restricted. As a result, diagnosis and treatment of the disorder often involves 'trial and error' on the part of the clinician.

Treatment of maladaptive pain in cats

In North America, there are no drugs approved for long-term use in cats with maladaptive pain, and only one NSAID (meloxicam) is approved for long-term use in some parts of the

world. Despite recent information suggesting that NSAID therapy can partly reverse central plasticity (Arendt-Nielsen et al., 2016), it is generally accepted that the maladaptive component of pain conditions is poorly responsive to NSAIDs (Edwards et al., 2016). Because there are also concerns around the potential for adverse effects from NSAIDs, interest in alternative drug therapy has emerged. Currently, drug choices are based on experience in people, or because of their activity on mechanisms shown to be important in rodent models of maladaptive pain. Medications that have been suggested for use in cats for the treatment of maladaptive pain are gabapentin, tramadol, amantadine, amitriptyline, tapentadol, flupirtine and anti-nerve growth factor antibodies (Table 1). This review outlines what is currently known about non-NSAID drug treatments that may be effective for chronic or maladaptive pain in cats.

Gabapentin

Gabapentin is an analogue of the neurotransmitter γ-Aminobutyric acid (Kukkar et al., 2013; Patel and Dickenson, 2016). Gabapentin exerts its effects on voltage-gated calcium channels, which are found on excitatory cells such as neurons. These channels respond to depolarization currents by allowing the influx of calcium ions (Dolphin, 2016). Four subunits of calcium channels have been identified, the main pore-forming α_1 subunit, and the accessory $\alpha_2\delta$, β, and γ subunits (Dolphin, 2016). Models of neuropathic pain have demonstrated an increase in the $\alpha_2\delta$-1 subunit in dorsal root ganglion (DRG) and dorsal horn neurons (Luo et al., 2001; Bauer et al., 2009). This subunit and binding target for gabapentin is responsible for guiding or trafficking of α_1 subunits and therefore pore assembly, indicating a vital role of the $\alpha_2\delta$-1 subunit in altered neuronal excitability and pain processing (Luo et al., 2001; Bauer et al., 2009; Dolphin, 2016; Patel and Dickenson, 2016). This binding results in a decrease in the influx of calcium ions

in response to an action potential, and therefore decreased neurotransmitter release or neuronal excitability. Gabapentin has been advocated for the treatment of neuropathic pain in veterinary species because of experience treating neuropathic pain in humans (Backonja et al., 1998; Kukkar et al., 2013; Moore et al., 2014; Larsen et al., 2016). In people it is only approved for postherpetic neuralgia, and as an adjunctive therapy for partial onset seizures, which are undocumented syndromes in animals.

The pharmacokinetics of oral (10 mg/kg) and intravenous (4 mg/kg) gabapentin in 6 adult spayed female cats has been described (Siao et al., 2010). While bioavailability varied greatly (range: 49.6 – 118.3%), potentially partially due to ad libitum feeding, the half-life after oral administration was approximately 3 h (177 ± 25 min), with peak concentrations ($C_{max)}$ values ranging from 4.6–10.6 µg/mL (Siao et al., 2010). Previously reported data and modeling suggests a half maximal effective concentration (EC50) ranging from 1.4 and 16.7 µg/mL for treatment of hyperalgesia in the rat (Taneja et al., 2012; Taneja et al., 2013; Larsen et al., 2016) and an EC50 of 5.4 µg/mL was estimated for humans with neuropathic pain (Lockwood et al., 2003). The authors then suggested a dosing regimen of 8 mg/kg every 6 h for an antihyperalgesia effect in the cat (Siao et al., 2010). However, caution is urged when extrapolating effective concentrations of the drug in cats based on pharmacokinetic-pharmacodynamic data from other species. There is also a current lack of information on pharmacokinetics after repeated dosing. Minimal or no plasma protein binding has been reported in other species, however this should be confirmed in the cat (Radulovic et al., 1995).

Currently, there are no clinical studies evaluating the efficacy of gabapentin in chronic pain conditions in cats. In a study evaluating the effects of gabapentin on nociceptive thermal thresholds in research cats (Pypendop et al., 2010), six female spayed adult cats received four dosages of oral gabapentin: 0 (placebo), 5, 10, and 30 mg/kg in a crossover design. Peak plasma concentrations ranged from 6.3 ± 1.3 µg/mL for the 5 mg/kg dosage, to 25.5 ± 8.6 µg/mL after administration of 30 mg/kg. Despite these plasma concentrations, there was no significant effect on thermal thresholds. This is not unexpected as the mechanism of action gabapentin suggests it would only show efficacy when α2δ-1 subunits are expressed in an abnormal, hyperalgesic state.

Several case studies describing the use of gabapentin exist (Vettorato and Corletto, 2011; Lorenz et al., 2012). One report details chronic use of gabapentin in three cats, following road trauma (*n*=2) or for musculoskeletal pain (*n*=1; Lorenz et al., 2012). Another case report details chronic gabapentin use after traumatic incidents (Vettorato and Corletto, 2011). In these case reports there was no objective or validated assessment of response. These individual uncontrolled case reports may not be helpful because of the high placebo effects in owner reports (Gruen et al., 2014; Gruen et al., 2017). Additional research evaluating safety and efficacy treating chronic or maladaptive pain is necessary before treatment recommendations should be made.

Tramadol

Tramadol is an opioid-like drug that exerts its effects via many different mechanisms of action including very weak µ-opioid effects, norepinephrine and serotonin reuptake inhibition, and binding of α2 adrenergic receptors in the pain pathway (Raffa et al., 1992; Faron-Górecka et

al., 2004). The drug is formulated with mixed enantiomers, each with slightly different effects. The first metabolite, M1 (o-desmethyltramadol), may be responsible for the majority of the analgesic effect in humans through opioidergic actions (Duhmke et al., 2004; Norrbrink and Lundeberg, 2009).

The pharmacokinetics of oral (5mg/kg) and intravenous (2mg/kg) tramadol in cats has been described (Pypendop and Ilkiw, 2007; Cagnardi et al., 2011). Oral bioavailability was reported as high, at 93% ± 7, with a terminal half-life of 4.82 ± 0.32hr for M1 (Pypendop and Ilkiw, 2007). The mean M1 C_{MAX} values after IV dosing were 0.37 and 0.81µg/mL (Pypendop and Ilkiw, 2007; Cagnardi et al., 2011). Both studies found a ratio of tramadol: M1 of ≥ 1, which contrasts with dogs which do not appear to produce the M1 metabolite (Giorgi et al., 2009). While more data needs to be collected about minimum effective concentration, the pharmacokinetic data collected so far is promising.

There have been two studies evaluating the efficacy of tramadol either alone, or in combination with meloxicam, in research cats with naturally occurring chronic OA-associated pain (Monteiro et al., 2016; Monteiro et al., 2017). In the first study, tramadol (3 mg/kg orally every 12 h) was compared against placebo in 15 meloxicam-treated cats (oral transmucosal preparation, 0.05 mg/kg every 24 h) with radiographically confirmed OA (Monteiro et al., 2016). Peak vertical force (PVF, expressed as % bodyweight), accelerometer-based motor activity (MA), and response to mechanical temporal summation (RMTS- determined by the number of subthreshold stimuli required for response) were measured at baseline, and after 21-25 days of treatment. The group found that while both cohorts showed improvement in PVF, cats receiving

only meloxicam showed improvement in motor activity, and only cats receiving both meloxicam and tramadol showed improvement (increase) in RMTS.

In the second study, 15 cats with radiographically confirmed OA, and five cats without OA were randomized to receive either placebo or tramadol (3 mg/kg PO every 12 h) for 19 days, with a crossover following a 3-month washout period (Monteiro et al., 2017). Outcome measures again included PVF, MA, and RMTS, though the PVF data set was incomplete due to technical problems. The group found that both PVF and RMTS were able to discriminate between normal and affected cats at baseline. They also found significant within and between-group increases in all outcome measures in OA-affected cats after treatment with tramadol (Monteiro et al., 2017). Mydriasis, sedation, hypersalivation, vomiting, and stomatorrhagia were observed in cats receiving tramadol (Monteiro et al., 2016; Monteiro et al., 2017). It is suspected that the reported bitter taste of the medication is responsible for the latter observations.

While additional research in a larger cohort of client-owned cats would be ideal, the pharmacokinetic data, and recent work suggesting that tramadol may help with maladaptive components of chronic pain is encouraging. Aversion to administration of medication may present a problem with clinical use, and may require compounding or reformulation.

Amantadine

Amantadine is used both as an antiviral medication (via unknown mechanism) in human medicine, as well as for treatment of Parkinson's, due to its modulatory effects on CNS dopamine concentrations (Hubsher et al., 2012). Amantadine has also been described as an N-

313 methyl-D- aspartate (NMDA) antagonist (Blanpied et al., 2005), resulting in its evaluation as an
314 analgesic (Bujak-Giżycka et al., 2012). The NMDA receptor, and its ligand, glutamate, have long
315 been implicated in the development and maintenance of central plasticity, via increased and
316 sustained excitation of neurons and subsequent alterations of gene and receptor expression
317 (Latremoliere and Woolf, 2009; Baron et al., 2013). Blockade of these receptors with NMDA
318 antagonists has been shown to both prevent the development of central plasticity, as well as treat
319 the condition in affected animals (Wang et al., 2015; Tabakoff et al., 2016).
320
321 Amantadine's use in cats stems from anecdotal reports of efficacy (Robertson, 2008a), or
322 from demonstrated efficacy in dogs when used in conjunction with the NSAID meloxicam
323 (Lascelles et al., 2008). In this latter study, amantadine was evaluated in dogs with OA that were
324 not fully responsive to NSAID therapy (maladaptive pain was suspected, though not specifically
325 assessed for), and found to be beneficial (Lascelles et al., 2008). While not indicative of
326 amantadine's efficacy as a sole analgesic, these data suggested promise when used as a part of
327 multi-drug therapy, or in NSAID refractory cases.
328
329 The pharmacokinetics of amantadine in six healthy adult female spayed cats has been
330 described (Siao et al., 2011b). Treatment groups included either 5 mg/kg administered orally or
331 an IV infusion of 0.5 mg/kg*min for 10 min. Oral absorption of the drug was complete. The
332 terminal half-life was calculated as 5.8 h and 5.4 h for IV and oral administration, respectively.
333 Time to maximal concentration (T_{max}) after oral administration ranged between 1.5 and 5 h, with
334 a C_{MAX} of 1.1 ± 0.1 µg/mL. Subsequent research aimed to evaluate amantadine's effect on
335 oxymorphone-induced thermal antinociception (Siao et al., 2011a). A constant rate infusion

(CRI) targeting the 1100 ng/mL C_{max} or an equivalent volume of saline were administered in combination with increasing oxymorphone CRI concentrations ranging from 0 to 0.4 µg/mL, chosen to approximate clinically relevant doses/concentrations (Siao et al., 2011a). Overall, there was no effect of amantadine on thermal thresholds, however, similar to gabapentin, amantadine may require changes present in the maladaptive pain state to exert appreciable effects. As no data exist for minimum effective concentrations, no dosing recommendations were made. The current recommendation is 3-5 mg/kg PO once daily according to other sources, likely derived from the work in dogs.

Amantadine's mechanism of action makes it an attractive candidate for further evaluation in cats. However, clinical data showing efficacy of amantadine is currently lacking.

Amitriptyline

Amitriptyline is a tricyclic antidepressant (TCA) that exerts its effect by inhibiting reuptake of the neurotransmitters serotonin, norepinephrine, and to a lesser effect, dopamine (Moore et al., 2012). It has also been shown to inhibit H1 release from mast cells in vitro (Gurgel et al., 2013). While its use in veterinary medicine has been limited primarily to behavioral disorders (Chew et al., 1998; Virga et al., 2001; Overall and Dunham, 2002), research in humans has demonstrated an analgesic effect in those suffering from interstitial cystitis (a urinary bladder disease with a chronic, neurogenic pain component; Hanno et al., 1989), and the drug is commonly used to treat neuropathic pain (Moore et al., 2012).

Due to the similarity of interstitial cystitis in humans, and idiopathic cystitis (IC) in cats, both proposed to have a neurogenic or neuropathic pain component, amitriptyline has been evaluated for efficacy in IC (Chew et al., 1998). Fifteen client-owned cats with severe, recurrent IC received 10 mg PO once daily, for up to 12 months in a non-blinded study. The number of cats reported to be free of clinical signs of disease at 6 and 12 months were 11 and nine, respectively. No changes in the cystoscopic examinations were apparent. It is thought that the clinical improvement, combined with the lack of changes in cystoscopy findings, indicates that amitriptyline's efficacy is limited to treatment of the pain and discomfort associated with the disorder (Chew et al., 1998). However, urinary retention secondary to amitriptyline's anti-cholinergic effect is another possibility. While placebo-controlled studies have evaluated amitriptyline's efficacy for the treatment of feline lower urinary tract disease (an umbrella term which includes IC), no benefit against placebo was appreciated (Kraijer et al., 2003; Kruger et al., 2003). However, these studies evaluated resolution of clinical signs of urinary disease after short term administration of the drug, so placebo-controlled data evaluating clinical signs of pain after long-term administration is still necessary.

The effect of amitriptyline on segmental inhibition, a physiological process that reduces the transmission of pain signals, was evaluated in 21 adult anesthetized cats (Fromm et al., 1991). The genders and breeds of the cats are not reported. The segmental inhibition of wide dynamic range neurons, which populate the dorsal horn and respond to all somatosensory inputs, was significantly increased by IV doses of 1.0 – 4.0 mg/kg of the drug, though no effect was seen on responsiveness to low-threshold mechanoreceptors. This may be beneficial with

maladaptive pain, where amitriptyline may be able to help correct the dysfunctional inhibitory processes of the CNS that have been demonstrated in models of maladaptive pain.

There are currently no data on the pharmacokinetics of amitriptyline in the cat, which would be important for making dosing recommendations. The drug's reported bitter taste, and potential side effects such as reduced grooming, sedation, and weight gain may limit its utilization (Chew et al., 1998). Validated, and if possible, objective measures should be used to establish efficacy for other chronic or maladaptive pain conditions in the cat before making treatment recommendations.

Flupirtine

Flupirtine is an aminopyridine drug, which is classified as a selective neuronal potassium channel opener (SNEPCO; Devulder, 2010; De Vito et al., 2014). The mechanism of action is via interaction with G-protein-regulated, inwardly rectifying K+ channels (GIRKs), a class of potassium channels separate from the voltage-gated family. Activation of GIRKs by flupirtine results in stabilization of the membrane potential by generation of a hyperpolarizing current, and thus, decreased neuronal excitability. Flupirtine also indirectly inhibits the NMDA receptor due to its role as an oxidizing agent at the receptor's redox site, which maintains the magnesium block on the NMDA receptor (Devulder, 2010; De Vito et al., 2014).

Flupirtine has historical use in Europe for a range of painful conditions in humans, including chronic pain, migraines, musculoskeletal back pain, myofascial pain, and for postoperative pain (Devulder, 2010; Harish et al., 2012). Opioid-sparing effects have also been

demonstrated. Unfortunately, acute hepatotoxicity (some cases requiring liver transplants) has been reported in humans (Douros et al., 2013).

Six healthy mixed breed adult cats (three male, three female) received single doses of flupirtine at 5 mg/kg IV and PO in one study (De Vito et al., 2014). The calculated bioavailability was 39.3 ± 9.7%, with a T_{MAX} of 2.78 h ± 0.77 after oral administration of the drug. The elimination half-life was reported as 13.67 ± 4.43 h after oral dosing, compared to an intravenous elimination half-life of 11.31 ± 2.24 h.

Some data exist for efficacy of the drug in an electrical tooth pulp model in dogs and cats, which revealed an ED50 of 3.5 mg/kg PO for dogs, and 3.0 mg/kg for cats (Gordon et al., 1987; Nickel, 1987). Unfortunately, the remaining evidence of efficacy is limited to non-companion animal models, including efficacy in different models of pain in rodents (Kolosov et al., 2012).

Flupirtine's novel mechanism of action makes it an attractive candidate for evaluation, though the drug's current availability in only European and Asian countries is a limitation.

Tapentadol

Tapentadol is part of a new class of drugs known as MORphine receptor agonist-Noradrenaline Reuptake Inhibitors (MOR-NRI), and shares structural similarities with tramadol (Pergolizzi et al., 2012; Taylor et al., 2013). Tapentadol's MOR affinity is 50-fold less than that of morphine, which appears to translate to a decrease in the typical opioid associated adverse effects such as pruritus, vomiting, decreased GI motility, and diarrhea (Pergolizzi et al., 2012). It

also only exists as a single enantiomer, and only the parent compound exerts the MOR-NRI effects, in contrast with tramadol. Some aspects of the drug, including its weak antimuscarinic effect, poor oral bioavailability, and weak 5-HT3 antagonism may impair its utility (Giorgi et al., 2012).

Tapentadol's disposition after IV, IM, and SC administration (5 mg/kg) in six healthy adult mixed-breed cats has been characterized (Lee et al., 2013). Bioavailability was high, at 93.93 ± 9.91% and 90.01 ± 6.52% for IM and SQ administration, respectively. Terminal half-life was calculated to be 2.93 ± 0.86 h, 2.28 ± 0.85 h, and 2.05 ± 0.6 h for IV, IM and SQ respectively. Side effects were similar to those previously reported in dogs (salivation, panting, etc.), though agitation was also seen in some cats, as is typical with opioids. There are some data evaluating the efficacy of orally administered tapentadol on thermal antinociception in cats (Doodnaught et al., 2017). Six healthy adult cats (4 females, 2 males) received either placebo, IM buprenorphine (0.02 mg/kg) or tapentadol (25 mg or 50 mg) orally in a randomized crossover study. Tapentadol was found to have a significant effect on skin thermal thresholds at 1 and 1-2 h (25mg and 50mg, respectively) when compared to baseline, but not when compared to placebo. This is contrasted to buprenorphine's efficacy at 1 and 2 h when compared against placebo. No pharmacokinetic data was collected or reported.

Currently, only parenteral routes of administration have been evaluated, with no data on potential efficacy in the cat. These data (oral pharmacokinetics and analgesic efficacy in the cat) are needed before any treatment recommendations can be made.

Maropitant

Maropitant is a potent and selective neurokinin-1 receptor (NK-1R) antagonist that functions as a central and peripheral anti-emetic (Hickman et al., 2008). This receptor is also shared by the ligand Substance P (SP), which has been studied for its role in inflammatory and nociceptive pathways (O'Connor et al., 2004). It is likely the knowledge that maropitant may have NK-1 antagonist activity, the known role of SP/NK-1 in pain and FDA approval for maropitant (Cerenia) in veterinary species has led to interest in evaluating the drug for analgesic effects.

The pharmacokinetics of maropitant administered both intravenously and orally (1 mg/kg) and of the drug administered subcutaneously (1 mg/kg) was evaluated in four mixed breed cats (Hickman et al., 2008). Oral bioavailability of the drug was low at 50%, while subcutaneous administration resulted complete absorption. Across the different routes of administration, the half life varied: 16.5, 13.1, and 17.1 h for IV, oral, and subcutaneous administration respectively. T_{MAX} values ranged from 2-3 h for oral administration, and 0.5 -2 h after subcutaneous administration, with corresponding C_{MAX} values of 156 ng/mL and 269 ng/mL respectively. Variability for these reported values were quite high, likely due in part to the small sample size.

The anesthetic-sparing effects of intravenous maropitant (1 and 5 mg/kg) was evaluated in 10 female cats using an ovarian stimulation model previously developed in the dog (Niyom et al., 2013). The study found a significant MAC reduction effect of both the 1 mg/kg and 5mg/kg

doses of maropitant, but they were not different from each other. However, it is important to note that MAC reduction cannot be assumed to translate into analgesia, as demonstrated by midazolam (Seddighi et al., 2011).

While initial pharmacological data are available, there is currently insufficient data for pain therapeutic recommendations to be made due to lack of efficacy data. Additionally, it is important to note NK-1 receptor antagonists have failed clinical trials for multiple painful conditions in humans (Hill, 2000). Possible causes for this include parallel pathways in the transmission of pain which reduce the importance of any one ligand or receptor, as well as a misinterpretation of anxiolysis as analgesia in pre-clinical animal data (Hill, 2000).

Future medications in development

Grapiprant

Grapiprant is a selective prostaglandin E receptor 4 (EP4) antagonist that is part of a new class of drugs, the piprants, which work by blocking prostaglandin E2 (PGE2) receptors (De Vito et al., 2016). Research has indicated that the EP4 receptor is important in mediating pain associated with both rheumatoid and osteoarthritis, as well as inflammation in general (St-Jacques and Ma, 2013). However, this mechanism of action can be considered similar to traditional NSAIDs, and so grapiprant may not be efficacious for pain syndromes with a primarily maladaptive drive.

While pharmacokinetic and clinical data of efficacy is available for dogs with osteoarthritis, only safety and toxicokinetic data are available in cats (Rausch-Derra et al., 2016; Rausch-Derra and Rhodes, 2016; Łebkowska-Wieruszewska et al., 2017). Grapiprant was administered to 24 healthy cats at doses ranging from 0 mg/kg to 15 mg/kg PO once daily for a 28-day period, with pharmacokinetic sampling occurring on Days 0 and 27. The half-life was quite variable, ranging from 2.08 ± 0.51 h in the 3 mg/kg male cat group on Day 0, to 14.12 h in the 3 mg/kg female cat group on Day 27. The reason for this wide disparity is unknown, but potentially related to the formulation (gel capsules) and prolonged residence in the GI tract of some cats. Significant accumulation was not seen, and there did not appear to be a relation between dosage and exposure. Minor clinical pathological abnormalities were reported, including changes in clotting times and hemoglobin, but not considered clinically relevant. Most importantly however, no GI or renal abnormalities were observed, in contrast to the concerns associated with the use of COX-inhibiting NSAIDs in cats. While the drug is still in early stages of evaluation in the cat, its potential as an anti-inflammatory, analgesic drug with an apparently good safety profile is encouraging. In the future, it is hoped that more robust pharmacokinetic and pharmacodynamic data become available, particularly studies of clinical efficacy in chronic pain conditions.

Anti-nerve growth factor antibodies

There has been a recent interest in inhibiting Nerve Growth Factor (NGF), a protein that regulates the growth, maintenance, and survival of neurons in the developing animal (Hefti et al., 2006; Chang et al., 2016). It is known that NGF levels are increased within the joints of humans and dogs affected by osteoarthritis (Halliday et al., 1998; Isola et al., 2011), where it can act to

increase sensitivity and excitability of nociceptors, in addition to stimulating the growth of new nerve fibers into inflamed tissue (Hefti et al., 2006; Chang et al., 2016). NGF has its actions via binding to a specific tyrosine kinase receptor (TrkA; Hefti et al., 2006). The resulting signaling cascade eventually produces changes in the transient receptor potential vanilloid receptor 1 (TRPV1) cation channel, which increases both the TRPV1 channel's excitability, as well as the production of other pro-excitation proteins (Hefti et al., 2006). NGF is also known to activate mast cells, whose cellular products can increase sensitization of neurons (Chang et al., 2016).

Both dog-specific and cat-specific (ranevetmab and frunevetmab, respectively) monoclonal antibodies against NGF have been developed, evaluated in pilot trials (Lascelles et al., 2015; Gruen et al., 2016), and demonstrated efficacy. Cats were required to have both chronic musculoskeletal disease and pain, based on physical, orthopedic, and radiographic examination, as well as owner-assessed pain or mobility impairment. Cats received a single injection of either 0.4 mg/kg or 0.8 mg/kg SC and demonstrated significant improvement compared to placebo in both objective measures of activity (accelerometer data) and subjective measures (veterinarian and owner assessments). In cats, the beneficial effect on activity was observed for 6 weeks. This is the first study that demonstrated an owner-assessed significant positive effect compared to placebo for chronic pain in cats. No adverse effects were reported. Currently, the role of anti-NGF antibody in treating central processes is unclear – we know that the biologic acts peripherally, but the robust efficacy suggests that there may be some modulation of central processes as well.

Pharmacokinetic data for NV-02 (the felinized antibody) is available for doses ranging from 2 mg/kg to 28 mg/kg SQ in 8 healthy cats (Gearing et al., 2016). T_{MAX} had a reported range of 1.9-4.3 days, and the half-life ranged from 7 to 15 days.

The data available for the felinizied anti-NGF antibody, including a long duration of action with few adverse effects, is promising. This biologic would be beneficial for cats in which oral administration of medications is not possible, or in cats where NSAIDs are not indicated. More pharmacologic and efficacy data are needed.

On a related note, development of anti-TNFα biologics have been reported, which may also be efficacious in maladaptive pain states, given the role of TNFα in maladaptive pain (Nexvet, 2016). However, insufficient information for discussion is available at this time.

Conclusions

Much is known about the neurobiology of chronic and maladaptive pain in rodent models, but conditions associated with maladaptive pain in cats have been recognized. Despite the interest in maladaptive pain in cats, assessing and measuring the pain still remains challenging and this hinders the assessment of putative analgesics. Treatment of chronic pain states in the cat thus remains a challenge, as only NSAIDs have extensively been clinically evaluated for long-term analgesia efficacy and safety. However, there are several drugs with mechanisms of action that make them attractive for the treatment of maladaptive pain, including gabapentin, tramadol, amantadine and others. More data on the pharmacokinetics and pharmacodynamics of these drugs in cats is needed to guide treatment.

Conflict of interest statement

Dr. Lascelles is a paid consultant for Aratana Therapeutics (grapiprant) and Nexvet (anti-NGF antibodies), and has received research funding from Nexvet. Drs. Adrian, Papich, Baynes, and Murrell have no conflicts of interest to disclose. None of the authors of this paper has any other financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Table 1

Drugs featured in this review and their mechanisms of action

Drug	Mechanism [a]
NSAIDs	COX 1 and/or COX 2 antagonism
Gabapentin	α2δ-1 subunit of voltage-gated calcium channels
Tramadol	μ-opioid receptor agonism, norepinephrine and serotonin reuptake inhibition, α-2 adrenergic receptor antagonism
Amantadine	NMDA antagonism
Amitriptyline	Serotonin, norepinephrine, dopamine reuptake inhibition
Flupirtine	G-protein-regulated, inwardly rectifying K^+ channel agonism, NMDA antagonism
Tapentadol	μ-opioid receptor agonism, norepinephrine reuptake inhibition
Maropitant	Neurokinin 1 receptor antagonism
Grapiprant	Prostaglandin E4 receptor antagonism
Frunevetmab	Antibody against nerve growth factor

COX, cyclo-oxygenase; NMDA, N-methyl-D-aspartate

[a] Generally accepted mechanism of action. There may be differences in the cat for some of the drugs dependent on metabolism

Figure legends

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.

Fig. 2. Schematic illustration of Maladaptive Pain. Neuropathic Pain – Physical damage to nervous system tissue (e.g. in this case, a tumor - yellow circle) results in very abnormal

922 activation of nociceptor sensory neurons – they become activated in response to previously sub-
923 threshold stimuli (blue circle). The subsequent pathway is as described in 'Adaptive' pain, but at
924 the level of the dorsal root ganglion (DRG) and the dorsal horn of the spinal cord there are
925 changes (nervous system plasticity) resulting in amplification of the signals and facilitation of
926 throughput of the signals. Additionally, the tonically active descending inhibition is less effective
927 (illustrated as a dashed green line), which again facilitates the signals being transmitted from the
928 periphery to higher centers. Hypersensitivity (increased pain from a stimulus that normally
929 provokes pain) and allodynia (pain due to a stimulus that does not normally provoke pain) occur
930 as a result of these changes, and in addition, spontaneous pain can occur due to abnormal activity
931 in the nervous system (e.g. generated at the site of nervous system injury).
932 A hallmark of 'neuropathic pain' is the presence of actual physical damage to part of the nervous
933 system and it is this that drives the changes in the way the system functions. Functional pain – In
934 Functional Maladaptive pain, the nervous system is grossly normal – there is no physical damage
935 of the system. However, the functioning of the system is abnormal. This abnormal central
936 processing results from repeated input to the system, causing nervous system plasticity (changes
937 in neurons and changes in the way supporting elements [e.g. microglia] communicate with
938 neurons) and thus amplification and facilitation of the processing of nociceptive information.
939 Under these conditions, a previously sub-threshold stimulus (blue circle) activates a physically
940 normal nociceptor (red line) but abnormal central processing in the spinal cord or brain (inset)
941 results in the stimulus being interpreted as painful. As with neuropathic pain, descending
942 inhibition may be defective (dashed green line).

Hypersensitivity (increased pain from a stimulus that normally provokes pain) and allodynia (pain due to a stimulus that does not normally provoke pain) occur as a result of these changes, and in addition, spontaneous pain can occur due to abnormal activity in the nervous system.

Figure 1 Adaptive Pain

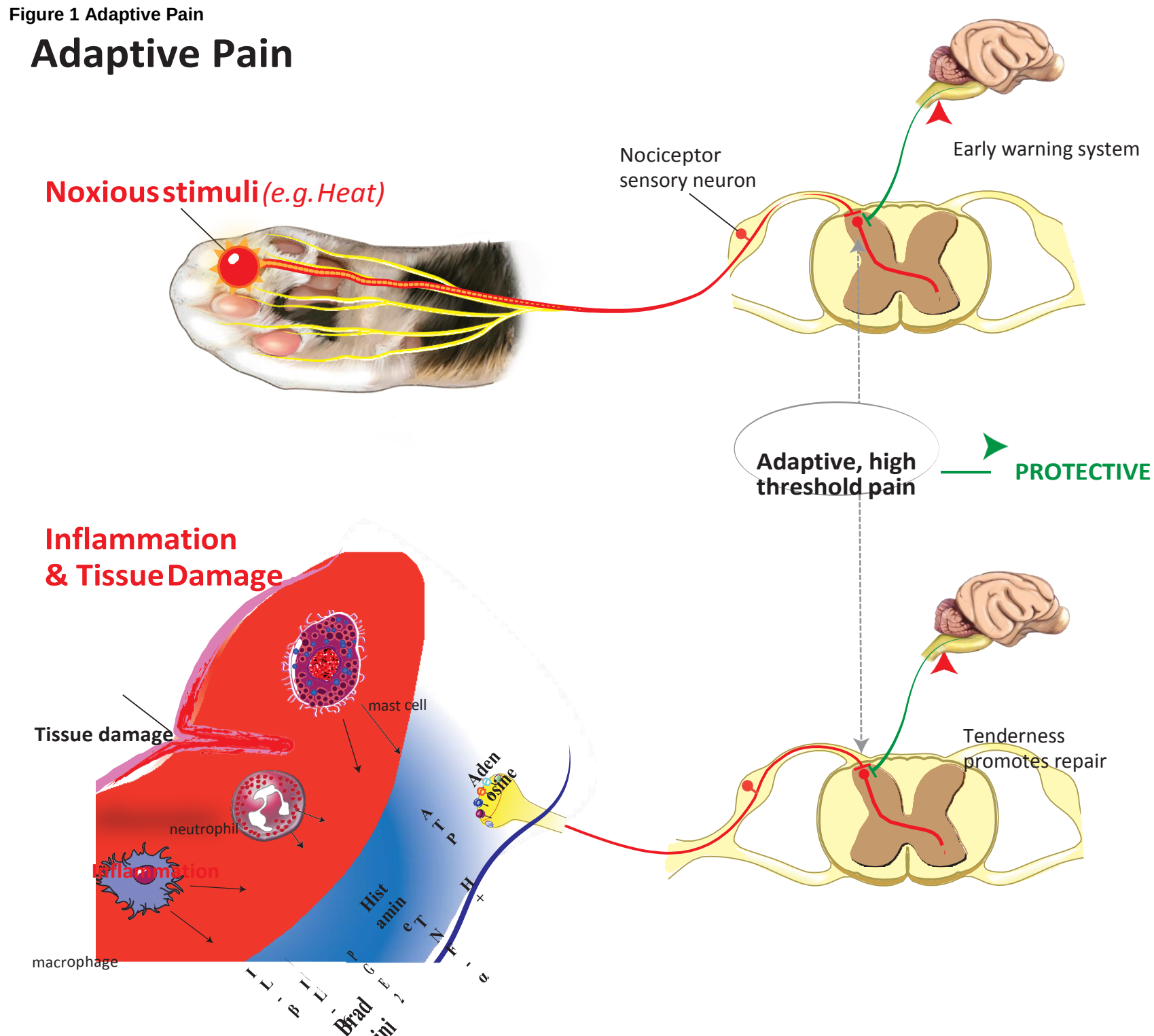
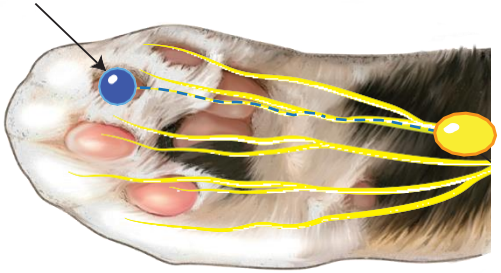


Figure 2 Maladaptive Pain

Maladaptive Pain

Neuropathic pain

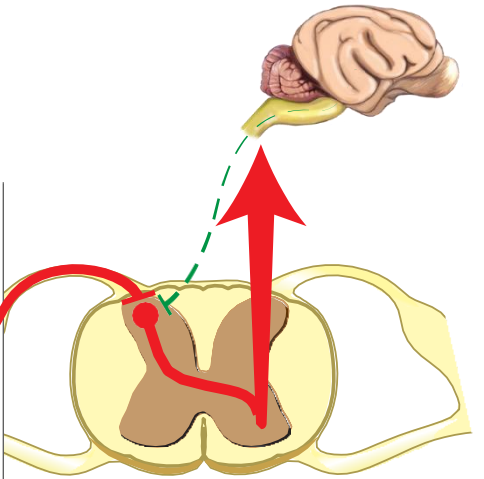
Normal low threshold stimuli



Nervous system structural damage
(e.g. peripheral nerve damage)

Neural lesion
(e.g. damage, tumor)

Nociceptor
sensory neuron

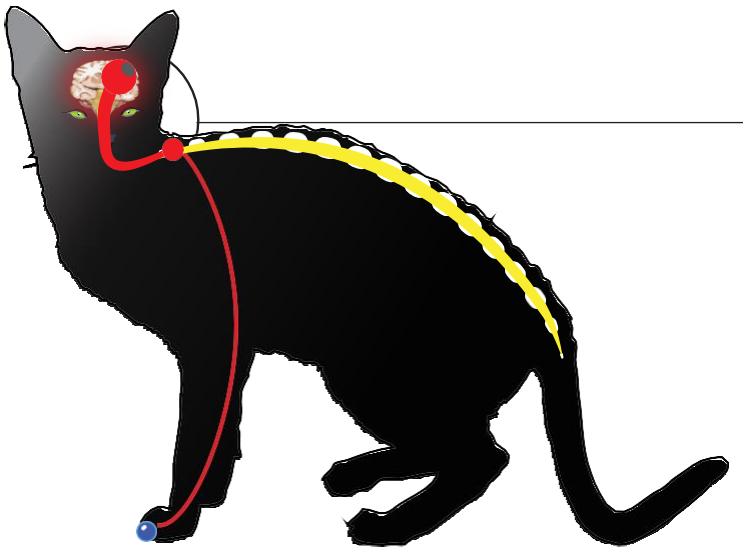


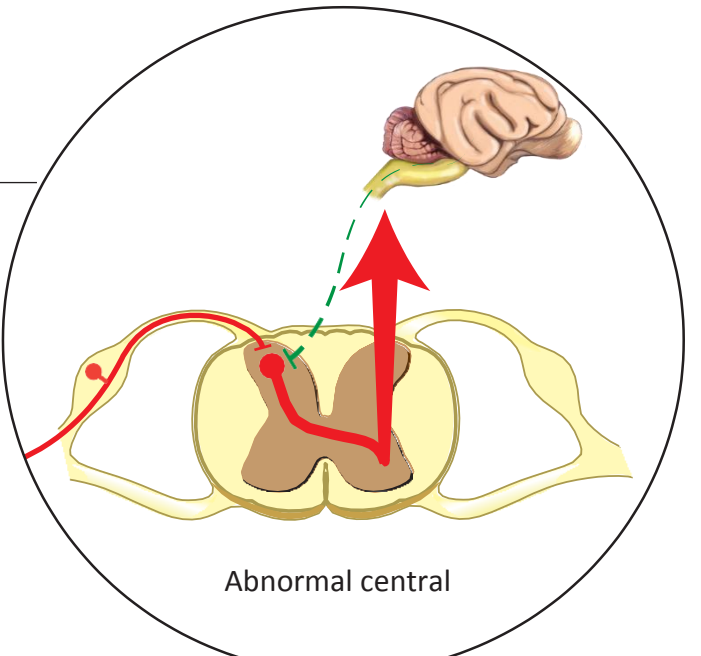
Abnormal central
(spinal cord or brain) processing

Maladaptive low-threshold pain

Hypersensitivity & Allodynia
Diseased state of the nervous system

Functional pain





Abnormal central

(spinal cord or brain) processing

Physically normal nervous system

Highlights

Chronic Maladaptive Pain in Cats: A Review of Current and Future Drug Treatment Options

- Maladaptive pain can involve actual damage to neural tissue and/or changes in nociceptive processing.
- Techniques like activity data, owner questionnaires, QST, and NWR may help in identifying maladaptive pain in the cat.
- Options for long-term pain control in the cat are lacking, with no drugs approved in North America, and one worldwide.
- While some data are available for potential therapies, most is limited to normal cats with poor measurements of efficacy.
- It is hoped that future research will yield a better understanding of maladaptive pain the cat and potential treatments.