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Guest Editorial

Assessment of animal pain and mechanism-based strategies for its reversal.

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More effective relief is required for chronic inflammatory or neuropathic pain in animals as many of the conventional analgesics have significant side effects. A timely review by Roy Meintjes (page …, this edition) helps to highlight this need by overviewing the pathways and mechanisms for processing pain in the nervous system – likely targets for analgesics of the future.

Progress in several areas is necessary to better define, treat and manage pain states thereby improving welfare in animals. These include: 1) accurate pain assessment using sensitive, reliable and refined methodology, 2) scientific understanding of the mechanisms of pain and novel targets for analgesia, 3) translational research for new treatments.

For effective pain management, the first key requirement is pain assessment by approaches that avoid subjective inferences. Repeatable and accurate assessments of animals using quantitative sensory testing (QST), forms a means by which the hypersensitivity likely to reflect chronic pain may be quantified. Such measures are especially useful for assessing those animals that might benefit from improved analgesic treatments. The tests involved have generally been adapted from those for clinical pain measurements in human patients. They are easy to use, assess readily recognisable withdrawal responses and involve brief stimuli just below or at threshold noxious levels in unrestrained animals. A systematic approach is important to assess the different components of pain. Horses with chronic laminitis can show changes in sensory nerves innervating the forelimbs (Jones et al., 2007) revealing that nerve damage as well as inflammation is present. Laminitic horses correspondingly show increased levels of sensitivity in response to deformation of the hoof wall, using a calibrated, computerised, mechanical pressure device (Vinuela-Fernandez et al., 2011). Such assessment helps monitor the diseases' progression and indicate that these animals suffer painful hypersensitivity to normally innocuous stimuli.

Similarly assessments of altered weight bearing and sensitivity to cutaneous stimuli in dogs with osteoarthritis have identified accentuated responsiveness to mechanical (using von Frey filaments) and cold temperatures in the affected limb (Brydges et al., 2012). These quantitative assessments form a necessary foundation for evidence based evaluation of whether an analgesic treatment is truly effective or not.

Secondly, an appreciation of the changes that occur in the peripheral and central nervous system during chronic pain is of considerable benefit when trying to deliver effective analgesia. Key transducers in peripheral sensory neurons can show alterations following different kinds of injury. The transient potential channel, TRPA1

is the leading candidate mediator of such cold-sensitive responsiveness (Kwan et al., 2006) and is notably facilitated by inflammatory mediators such as prostaglandins, bradykinin and inflammatory proteases (for example, (Bandell et al., 2004). Rapidly accumulating evidence is pointing towards TRPA1 as being an important mediator of mechanical hypersensitivity in chronic pain models (Kwan et al., 2009). Cold- and pressure-sensitive mediators in joint afferents contributing to hypersensitivity may include TRPA1 (McGaraughty et al., 2010). Changes in responsiveness to warm as well as to cold thermal stimuli in inflammatory conditions suggest that other mediators such as TRPV1 may also play a role and correspondingly, expression of TRPV1 is upregulated in osteoarthritis and following sensory nerve damage (Facer et al., 2007; Fernihough et al., 2005). Such channels may represent targets for future analgesics that can effectively treat pain hypersensitivity in a clinical setting.

Further, as Roy Meintjes describes, there are also a number of important changes in the initial relays within the spinal dorsal horn that contribute to hyperexcitability. The increased spinal excitability can be transmitted to higher regions of the brain, thereby leading to accentuated perception of pain. At the spinal level, excitatory amino acid receptors, such as the NMDA receptor, linking with intracellular adapter molecules eg postsynaptic density-95 (PSD-95), can interact with signalling molecules to enhance processing and are important for sensitisation (Arbuckle et al., 2010; Garry et al., 2004). Enhanced transmission through the pain pathways at the level of the spinal dorsal horn will result. The AMPA receptor is also important in this process, as it is thought to be trafficked into synapses together with metabotropic glutamate receptors (mGluR) during chronic pain states (Garry and Fleetwood-Walker, 2004; Young et al., 1998). In the central nervous system longer term changes are highly likely following sensory afferent activation if the injury remains unresolved for a prolonged period of time. In early disease states or after surgical injuries, pre-emptive treatment may provide an opportunity to reduce these types of sensitisation events in the nociceptive processing pathways. Administration around the time of the initial injury, of an NMDA receptor antagonist, eg memantine or ketamine, appears to be more effective in preventing sensitisation than retrospective intervention (Wilson et al., 2005).

One mechanistic issue to consider in chronic pain is that changes occurring in gene expression within sensory neurons may diminish the effectiveness of conventional analgesics. Neuropathic pain for example is notably resistant to many analgesics such as opioids. One reason may be that different neurotransmitters such as the neuropeptide vasoactive intestinal polypeptide (VIP) become expressed in injured primary sensory neurons, while their receptors such as the $VPAC_2$ receptor show increased expression in spinal cord neurons (Dickinson and Fleetwood-Walker, 1999). Such injury-specific events may represent refined targets for the design of novel analgesics.

Finally it is important to consider that not only laboratory-based investigations but also the experience gained from their translation into human clinical medicine can give insights into new ways of treating animal pain. For example it was only recently established that activation of the TRPM8 ion channel in a subpopulation of primary sensory neurons reflects a novel and highly effective endogenous mechanism for chronic pain relief (Fleetwood-Walker et al., 2007; Proudfoot et al., 2006). This can be achieved by topical application of selective TRPM8 activators such as menthol and is effective for both inflammatory or nerve damage situations. Topical administration of TRPM8 activators may form the basis of a new treatment strategy for chronic pain in both man and in animals. Early trials in human clinical

settings are already providing promising evidence in support of its efficacy (Colvin et al., 2008; Storey et al., 2010).

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