Can a focus on translatability in preclinical pain research benefit research animals?

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Summary

Pain is a condition of widespread clinical significance and animals are used to investigate underlying mechanisms and potential treatments. Research has led to a rapid increase in the knowledge of mechanisms but not in the available therapies for clinical pain syndromes. Methods are being explored to improve translation, including increasing similarity to clinical conditions. For example, therapies for persistent post-surgical pain (PPP), a malignant condition in which pain continues after the surgical wound has healed, are being developed in animal models. Patients that develop this condition usually receive opioids to manage postoperative pain, but the rodent models often do not. To better replicate the clinical condition, and potentially improve translatability, postoperative opioids could also be provided to the research animals. Additionally, postoperative opioids may provide a measure of pain relief to the experimental animals leading to refinement of preclinical PPP research.

Keywords: pain, neuropathic pain, analgesia, refinement, translation

1 Introduction

Ethics: Pain and the Three Rs

The Canadian Council on Animal Care (CCAC) is the national body that oversees the ethical use of animals in science (CCAC, 2011). The principles of humane science, or the Three Rs (replacement, reduction and refinement of animal use – Russell and Burch, 1959), are an integral part of the CCAC's policy on the ethics of animal investigation (CCAC, 1989). According to the Three Rs tenet, the pain and distress experienced by experimental animals must be minimized (refinement). Thus, investigators have a moral responsibility to prevent and alleviate pain by reducing its intensity and/or duration (ILAR, 2009). While all animal research requires ethical consideration and adherence to the Three Rs, where the potential costs to the animals (in terms of pain and distress) are high, for example pain research, studies must have a high likelihood of benefit to offset the animal suffering (Bateson, 1986; ILAR, 2009). In order to maximize the potential benefit there is, perhaps, a greater need for emphasis on translation of pain research.

Managing pain in laboratory animals?

As a result of experimental procedures, laboratory animals may experience pain that can be managed using both preventive and therapeutic measures (ILAR, 2009). Management strategies include the administration of anesthetic agents, sedatives or anxiolytics, and analgesics where necessary, in addition to handling and husbandry techniques, as well as the refinement of experimental techniques (ILAR, 2009). When pain is the phenomenon under study, the management of pain is subject to particular challenges. Treating pain during the experimental procedure would invalidate the outcome measures, where experimental outcomes are the behavioral responses to painful stimuli or, when exploring a novel analgesic, the effect of the compound of interest on the behavioral responses to painful stimuli. In addition, any treatment that modifies the experience of pain has the potential to interfere with the development of the pain model itself (Simkins et al., 1998).

Animals often undergo painful procedures that involve extensive tissue manipulation in order to generate models of chronic pain in which outcome measures will be used (Simkins et al., 1998; Stewart and Martin, 2003). As a result, animals may experience pain that is not directly related to the condition being studied or the outcome measures of interest. Managing the pain that is related to model development may or may not affect the outcome measures depending on the management strategies chosen and the timing of model induction versus the measurement of outcomes (Simkins et al., 1998). In order to understand the potential for refinement, it is important to understand pain and the typical approaches to its study.

2 What is pain?

The international association for the study of pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." The experience of pain is considered to be more than simply nociception, including consideration for how a particular stimulus or sensation is perceived. Pain can be grouped into four categories: nociceptive pain, inflammatory pain, neuropathic pain, and dysfunctional pain (Costigan et al.,

2009). Nociceptive and inflammatory pains are protective, occurring in the presence of a stimulus with the potential to cause tissue damage or following tissue damage in association with the subsequent inflammatory response (Costigan et al., 2009). Dysfunctional and neuropathic pains are clinical syndromes that persist in the absence of any evident stimulus (Costigan et al., 2009). The IASP defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." As evidenced from the broad definition, there are many different etiologies and manifestations of neuropathic pain (Dworkin et al., 2007) and it is characterized by a variety of symptoms, including pain in response to a normally innocuous stimulus (allodynia) and exaggerated pain in response to a normally painful stimulus (hyperalgesia) as well as spontaneous pain, and other sensory abnormalities (Backonja, 2003; Costigan et al., 2009).

Persistent post-surgical pain: A human condition modeled in laboratory animals

Persistent post-surgical pain (PPP) is a malignant condition well described by Kehlet et al. (2006). Briefly, 10-50% of patients develop PPP following various surgical procedures. It is characterized by pain that persists, with no evident cause, after the surgical incision and associated inflammation have healed. In the majority of patients, it has been hypothesized that surgical injury of peripheral nerves leads to central and peripheral nervous system changes that result in the development of neuropathic pain, since neuropathic pain and PPP share similar symptoms. Once established, neuropathic pain is difficult to treat – 40 to 60% of patients obtain partial pain relief from available therapies (Finnerup et al., 2005; Dworkin et al., 2007). Therefore, preclinical research is needed in order to identify novel targets for the treatment and prevention of neuropathic pain (Dworkin et al., 2007). Patients generally receive opioids, often administered in conjunction with non-steroidal anti-inflammatory drugs (NSAIDs), for the management of moderate-to-severe acute postoperative pain (Carr and Goudas, 1999; Myles and Power, 2007; Krenzischek et al., 2008) in the same time frame as the insult that gives rise to PPP occurs. While there are issues related to the translation of acute postoperative pain, some of which arise from the fact that treatments provided are individualized and context-sensitive (Dahl et al., 2010), this paper is limited to a discussion of the translatability of neuropathic pain research.

Animal models of neuropathic pain

Animal models are considered to have contributed significantly to the understanding and treatment of chronic pain (Wang and Wang, 2003) and continue to be used to study the underlying mechanisms of and potential treatments for neuropathic pain (Wang and Wang, 2003; Sorkin and Yaksh, 2009). A variety of neuropathic pain models have been developed in an effort to replicate the different etiologies of clinical pain syndromes; these include models of cancer pain, central and peripheral nerve injury, and neuropathies induced by viral or metabolic diseases (Wang and Wang, 2003). Many neuropathic pain models are surgically induced, requiring extensive tissue manipulation and resulting in postoperative pain (Simkins et al., 1998; Stewart and Martin, 2003). One of these models, the spared nerve injury (SNI) model, is a model of partial denervation (produced through injury to two out of the three terminal branches of the sciatic nerve) resulting in rapid onset of sensory changes with a long duration including: heat hyperalgesia, cold allodynia, mechanical allodynia and hyperalgesia, (Decosterd and Woolf, 2000) and chemogenic hyper- and hyposensitivity (Meisner et al., 2008). The etiology (mechanical injury) and the reliability, long duration and broad spectrum of the sensory changes mean that the SNI model is a useful starting point for the exploration of PPP.

3 Challenges in Translation

Preclinical pain research

The translation of preclinical animal-based research into human clinical therapies is challenging for many areas of scientific research. Research has led to a substantial increase in the knowledge of pain mechanisms over the last decade but little development of new treatments for pain, particularly chronic pain (for review see Langley et al., 2008; Mogil, 2009; Mogil et al., 2010). Drugs that have been developed where animal models have predicted efficacy for the treatment of pain have often failed to pass clinical trials as a result of lack of efficacy or unpredicted adverse effects in humans (Langley et al., 2008; Mogil, 2009; Mogil et al., 2010). The high profile drug failure of Neurokinin (NK)-1 receptor antagonists, for example, has led many to question the utility of animal models in pain research as well as the clinical relevance of the testing methods used in this discipline (Hill, 2000).

Factors that may influence translation

Many factors can influence the experience of pain and the development of pain syndromes (Langley et al., 2008; Costigan et al., 2009; Mogil, 2009; Mogil et al., 2010). The failure of preclinical pain research to replicate some fundamental aspects of clinical pain syndromes has been highlighted as a challenge for translation (Langley et al., 2008; Mogil, 2009). Translation is thought to be limited by many factors, including the choice of subjects (i.e. species, strain, and sex), current models, and outcome measures (Langley et al., 2008; Mogil, 2009, Mogil et al., 2010). Briefly, as outlined by Mogil (2009), while species differences always limit translatability from animal to human, the subjects chosen, including individual characteristics and strain, within the laboratory species can also affect the potential for translatability. In the clinic, chronic pain conditions are more common in women and in the aged population with varied genetic backgrounds; however, animal experiments are carried out almost exclusively with young, male rats of a single strain (there exists a marked difference in pain presentation and analgesic effects across strains of the same species, old versus young, and male versus female rats). This failure to represent the clinical population may contribute to the limited translatability of pre-

clinical pain research. Furthermore, the outcome measures that are used most often in animal studies do not match up with the most common symptoms in clinical pain syndromes, an additional mismatch that may impact translatability (Langley et al., 2008), although alternative outcome measures exist or are being developed (Mogil et al., 2010).

Translation and PPP

PPP is a good candidate research area for pilot studies to improve translation. The timing and nature of the insult that gives rise to PPP are predictable since PPP is, by definition, chronic pain that was initiated at the time of a surgical procedure. The chronic pain condition arises from mechanical injury to a nerve and the management of perioperative pain is a known factor at the time of nerve injury. The SNI model replicates this condition well in terms of the type of insult and the ability to manage pain at the time of surgery to induce the model. Currently, postoperative analgesics are often withheld when generating the SNI model (Stewart and Martin, 2003). Managing postoperative pain upon model induction may better represent the clinical condition and help to improve translation.

The potential for refinement

Pilot studies could be instrumental in applying an 'incremental approach' to the refinement of chronic pain studies. For example, in the case of PPP, postoperative opioids may be administered since they are the mainstay for managing moderate-to-severe postoperative pain in the clinical setting (Carr and Goudas, 1999; Myles and Power, 2007; Krenzischek et al., 2008). Following implementation of pain management strategies arising from this research, it may be possible to explore the effects of multimodal analgesia on experimental outcomes, further increasing the similarity to clinical postoperative pain management (Myles and Power, 2007; Pyati and Gan, 2007; Krenzischek et al., 2008). The desire to increase translatability may help to refine preclinical exploration of PPP by alleviating postoperative pain. Furthermore, if postoperative analgesia is shown to have no effect on model development and experimental outcomes, the dosage could be optimized and applied to other areas of pain research, beginning with similar models. Continued use of pilot studies could help to validate refinements (Auer et al., 2007; Fenwick et al., 2010; Fenwick et al., 2011).

Evidence exists for the provision of postoperative analgesia in the SNI model in the literature (Stewart and Martin, 2003; Arsenault and Sawynok, 2009). Arsenault and Sawynok (2009) studied the effects of amitriptyline on the development of neuropathic pain in the SNI model endeavoring to find a drug with the potential to prevent the development of PPP. Earlier in the study, amitriptyline, which is currently used for the treatment of established neuropathic pain in the clinical setting, was found to attenuate the development of long-term hypersensitivity to a chemical stimulus when administered in the perioperative period. Since patients often receive postoperative morphine, a pilot study was conducted to see whether postoperative morphine would interfere with the experimental outcomes. The administration of postoperative morphine did not significantly alter the preventive effects of amitriptyline in the SNI model; the experimental outcomes were preserved. Another study, by Stewart and Martin (2003), investigated the effects of a number of analgesics, including one opioid, fentanyl, on the development of sensory changes characteristic of the SNI model. Fentanyl did affect the sensory changes on the days where it was administered, and, of all the endpoints studied, only affected dynamic allodynia after drug administration had ceased. Research conducted using the Chung model of neuropathic pain found that mechanical allodynia developed in spite of the administration of postoperative analgesics; however, the time course was altered by certain drugs (Simkins et al., 1998). It is yet to be determined whether the data derived from studies where postoperative analgesics have been used in the generation of a nerve injury model improve translatability. The utility of these findings will be influenced by many experimental factors and must be approached with caution as evidence exists that postoperative analgesics may influence model development under certain circumstances (For example, Puke and Wiesenfeld-Hallin, 1993; Decosterd et al., 2004; Rashid and Ueda, 2005; Horvath et al., 2010).

4 Conclusion

Animals used in pain research may be at risk for experiencing a higher degree of pain and distress than animals used in research in other disciplines. Perhaps as a result, pain investigators are particularly focused on improving the models and outcome measures used in preclinical research in an effort to improve translatability. These efforts to improve translation also have the potential to enhance the implementation of the Three Rs. Pilot studies are a useful tool to explore the effects of pain management strategies on experimental outcomes. Accumulation of data on pain management strategies in a variety of models may allow for the determination of the degree and type of pain management that is appropriate for a particular model and experimental outcome, leading to a reduction in pain experienced by the animals used. Furthermore, increased translation may help to reduce the number of animals used in pain research also enhancing implementation of the Three Rs.

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