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Use of spontaneous behaviour measures to assess pain in laboratory rats and mice: How are we progressing?

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ABSTRACT

The understanding and recognition of pain in laboratory rats and mice has advanced considerably in recent times. However, there is evidence that despite these advances, analgesics are still relatively underutilised in these species. One possible contributing influence to this is the difficulty in assessing pain reliably and objectively in these prey species. This review presents the current scientific knowledge on behavioural methods of pain assessment in laboratory rats and mice. The focus is on measures of spontaneous behaviour, since these will find greatest utility in clinical pain management.

A range of behavioural pain assessment tools are discussed and difficulties in study interpretation are highlighted. Such methods include locomotor activity, pain specific behaviour identification and the novel facial pain recognition methods developed more recently. Practical problems associated with the techniques are discussed and gaps in the scientific knowledge are identified. A substantial body of information on behavioural signs of acute pain has been collected. Developing awareness and attention to this amongst research workers would improve its application to practice. However, use of techniques for objective measurement can be laborious, subject to variability and confounded by experimental procedures. The increased availability of automated behavioural monitoring systems will reduce these concerns, but it still remains imperative that researchers perform behavioural pilot studies to elucidate behaviours of interest specific to their animal model.

Few murine studies of behavioural pain assessment have been performed and this is an area that needs further investigation. Additionally, whilst acute post-operative pain scales in rats have been fairly well-characterised, these should be tested in different acute pain models to determine their reproducibility. Few tools for assessment of chronic pain, such as that arising from inflammatory or neoplastic disease, exist in both of the species examined. Pain-specific behavioural identification is the more widely tested method in the face of chronic pain. However, studies to date have yielded few reliable and consistent behaviours indicative of this category of pain. This is an area in which future studies and funding should be directed, given the significant number of laboratory animals that are likely to experience such pain states. Greater collaboration between ethologists and scientists using animal models should be established in order to improve animal welfare and advance scientific knowledge in this area.

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1. Introduction

An unfortunate outcome of many scientific procedures performed on laboratory animals is their experience of pain and distress. This could be as a result of surgical manipulation, induction of disease or through genetic alteration. In addition to the resultant welfare cost, there may be a confounding effect on research data brought about by a change in physiological variables. Therefore, prevention and alleviation of pain through accurate pain assessment and appropriate analgesic use should be a priority for those in the laboratory animal science field. In addition to these animal-based considerations, animal model development remains critical in the field of pain research and there is a rapidly expanding market for novel therapeutic agents which target pain. Whilst the outcome measures in the preclinical testing of these agents has traditionally included withdrawal reflexes elicited by acute stimulation (Mogil et al., 2010a), these methods do not measure cognitive appraisal, the subjective view of the overall pain experience (Cobos et al., 2012). In fact, despite the advancing sophistication of animal injury models, evidence suggests that dependent measures of pain behaviour have remained largely unchanged since 2000 (Mogil and Crager, 2004). This is a surprising finding given that the emotional element of pain is likely to be of most concern to human patients.

The recognition of pain in animals has traditionally been done subjectively through the application of clinical reasoning and the use of preconceived notions of appearance and behaviour (Recognition and Alleviation of Pain in Laboratory Animals, 2009). Such methods are likely to be effective for recognition of severe pain. Additionally, changes in successive observations recorded by a single observer remain valid in determining an improvement or deterioration of condition, even though many of the criteria used may not be a specific response to pain. However, a lack of generally accepted criteria for pain blights the assessment of more insidious pain states, especially in rodent-prey species that are more likely to mask their pain responses as part of a survival mechanism (Mayer, 2007; Stasiak et al., 2003). Objective pain assessment techniques have been developed in a range of animal species (Flecknell and Liles, 1991; Liles and Flecknell, 1993; Malavasi et al., 2006) but typically the measures used involve retrospective assessment, through analysis of stored behavioural data once the experiment has concluded. This clearly does not allow for alteration to analgesic regimes. More recent behavioural analysis techniques show promise in this regard being increasingly recognised as effective "cage-side" pain assessment tools (Roughan and Flecknell, 2001; Wright-Williams et al., 2007).

Whilst considerable progress has been made in determination and validation of pain assessment tools for use in acute pain states such as in the immediate post-operative period, there remain few consistent and reliable tools for use in chronic pain models. With the latter category likely to make up a significant proportion of the animals used in biomedical research this is perturbing. The major hindrance to development of chronic pain scales relates to the specific identification of pain behaviours as opposed to general malaise (Mogil and Crager, 2004), and an overall reduction of activity (Roughan et al., 2004), necessitating extended monitoring periods and more frequent observation bouts.

The aim of this review is to provide individuals working in the laboratory animal science field with an overview of behavioural techniques that might be applied to evaluate spontaneous pain behaviours in rats and mice. The focus is on spontaneously emitted behaviours rather than analgesiometric methods since the former are likely to have greater clinical application, and more accurately model the assessment of pain in human clinical trials. Their non-invasive nature also allows easier incorporation into studies due to reduced ethical concerns, although, they may not be completely devoid of welfare cost, since animals may be exposed to an unfamiliar environment and experience fear and apprehension (Wright-Williams et al., 2007). Controversial aspects and those areas requiring further elucidation are highlighted.