Applied Animal Behaviour Science 163 (2015) 19–27

Contents lists available at ScienceDirect

Applied Animal Behaviour Science

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

Review

The power of automated behavioural homecage technologies in characterizing disease progression in laboratory mice: A review

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ARTICLE INFO

Article history:
Accepted 26 November 2014
Available online 11 December 2014

Keywords:
Animal welfare
Automated behavioural analysis
Disease
Humane endpoints
Mice
Replacement, reduction, refinement (3Rs)

ABSTRACT

Behavioural changes that occur as animals become sick have been characterized in a number of species and include the less frequent occurrence of 'luxury behaviours' such as playing, grooming and socialization. 'Sickness behaviours' or behavioural changes following exposure to infectious agents, have been particularly well described; animals are typically less active, sleep more, exhibit postural changes and consume less food/water. Disease is frequently induced in laboratory mice to model pathophysiological processes and investigate potential therapies but despite what is known about behavioural changes as animals become sick, behavioural phenotyping of mice involved in disease studies is relatively rare. A detailed understanding of how behaviour changes as mice get sick could be applied to improve welfare of laboratory mice and support the underlying biomedical research. Specifically, characterizing behavioural changes in ill health could help those working with laboratory mice to recognize when refinements should be introduced, when severity limits are being approached and when humane endpoints should be implemented. Understanding how behaviour changes with illness may also help to identify compounds that have a clinical effect as well as when these agents act. There are an increasing number of automated systems to monitor the behaviour of laboratory mice in their homecages incorporating technologies such as the quantification of cage movement, automated video analysis and radiofrequency identification transponders/readers. Mouse models of neurodegenerative diseases particularly Huntington's disease have been well characterized using these systems and behavioural biomarkers of pathology, including changes in the animals' use of environmental enrichment, changes in food/water consumption and alterations in circadian rhythms, are now monitored by laboratories worldwide and used to refine studies and develop therapies. In contrast, automated behavioural technologies have not been used to characterize the behaviour of mice with systemic diseases such as cancer and liver disease. In this review, common behavioural changes that occur in animals with declining health will be discussed with an emphasis on progressive disease studies involving mice. Automated homecage behaviour recording technologies will then be summarized, studies in which these systems have been used to characterize the behaviour of mice with progressive diseases will be reviewed and the potential to apply automated technologies to refine disease studies involving mice will be discussed.

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http://dx.doi.org/10.1016/j.applanim.2014.11.018
0168-1591/

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1. Introduction

Laboratory mice (*Mus musculus*) are the most commonly used animals in scientific research; in 2012 74% of scientific procedures carried out on animals within the UK involved mice (Home Office, 2013). In many experimental studies involving mice, disease is induced to model pathophysiological processes and investigate potential therapeutic agents. In accordance with Russell and Burch's 3Rs Principles, when planning a study which would potentially involve the experimental use of animals we should always aim to *replace* laboratory animals with non-sentient alternatives, *reduce* the number of animals used and *refine* experimental procedures to minimize pain and distress (Russell and Burch, 1959). Although there are sometimes unavoidable costs to mice used in disease studies, measures can often be implemented to refine experimental procedures and alleviate pain and/or distress (Committee on Recognition and Alleviation of Distress in Laboratory Animals, 2008). Examples of potential refinements to experimental procedures include the provision of additional care during critical periods of a study, use of the least severe animal experimental model when several models could be used to address a scientific question, improvements to husbandry as well as adherence to both pre-defined severity limits and appropriate humane endpoints.

In progressive disease studies severity limits and humane endpoints are likely to be particularly important in limiting pain and distress (Olsson et al., 2008; Franco et al., 2012a,b; Ashall and Millar, 2013, 2014; Jirkof et al., 2013). Severity limits or justifiable humane endpoints can be defined as a pre-determined set of ethical criteria that allow those working with laboratory animals to recognize when the benefits of the scientific experiment are outweighed by welfare costs to the animal (e.g. the point where the potential scientific benefits of a study are outweighed by the pain or distress induced, EU, 2010). When severity limits/justifiable humane endpoints are met interventions such as analgesic administration or humane killing can be carried out (EU, 2010; Ashall and Millar, 2014). Scientific humane endpoints refer to criteria that allow early termination of experiments before animals experience significant harm while still meeting the experimental objectives (NC3Rs, 2013; Ashall and Millar, 2014). In disease studies, when pain and/or distress are more likely to occur as conditions progress, scientific humane endpoints are implemented to limit disease severity to the minimum required to address an experimental question. Unfortunately both objectively assessing animal welfare and non-invasively measuring disease progression are challenging and can therefore be obstacles to refining disease studies involving mice. Imaging is often advocated as a minimally invasive method of tracking disease progression (Hudson, 2005; Committee on Recognition and Alleviation of Distress in Laboratory Animals, 2008), but anaesthesia is typically required which may affect experimental outcomes and have a welfare cost (Wong et al., 2013). Identifying further behavioural biomarkers of disease progression through cooperation between biomedical scientists and ethologists (Broom, 2006) could therefore help to refine disease studies involving mice. There are also likely to be considerable biomedical benefits to characterizing behavioural changes that occur with disease. There has been increasing concern about animal studies translating poorly to human patients with a contributing factor being that animal studies do not always sufficiently reflect disease in humans (van der Worp et al., 2010). Identification of the mouse models of disease that more closely replicate human disease phenotypes may improve their predictive validity (McGonigle and Ruggeri, 2014). The further use of behavioural analyses to then identify therapies that have a clinical effect on mice may also increase the likelihood of effective translation of studies involving mice to human patients.

The aim here is to review behavioural changes with ill health in mammals with an emphasis on studies involving mice. The potential role of automated homecage behavioural monitoring technologies for characterizing behavioural changes in mice with progressive disease and refining disease studies will then be summarized. Compared to behavioural changes that occur with progressive disease, the automated detection of behavioural changes that occur in pain states have been relatively well described (e.g. Roughan et al., 2009; Miller et al., 2011, 2012; Urban et al., 2011; Wright-Williams et al., 2013; Whittaker and Howarth, 2014), and will therefore not be discussed further here.

2. How does the behaviour of animals change with ill health?

Behavioural changes that occur with ill health have been characterized in a number of species with a range of pathologies. A particularly well characterized series of symptoms collectively referred to as 'sickness behaviours' is frequently seen in animals challenged by infectious