European Journal of Pharmacology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

The pain of pain: Challenges of animal behavior models

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ARTICLE INFO

Article history:
Accepted 26 November 2014

Keywords:
Berend Olivier
Animal models
Pain
Biomarkers
Sigma1
Translational research

ABSTRACT

Berend Olivier has had a long-standing interest in the utility of animal models for a wide variety of therapeutic indications. His work has spanned multiple types of models, blending ethological, or species typical and naturalistic behaviors, along with methodologies based on learned behavior. He has consistently done so, from an analytical as well as predictive perspective, and has made multiple contributions while working in both the pharmaceutical industry and within an academic institution. Although focused primarily on psychiatric disorders, Berend has conducted research in the area of pain in humans and in animals, demonstrating an expansive appreciation for the breadth, scope and significance of the science and applications of the discipline of pharmacology to these diverse areas. This review focuses on the use of animal models in pain research from the perspective of the long-standing deficiencies in the development of therapeutics in this area and from a preclinical perspective where the translational weaknesses have been quite problematic. The challenges confronting animal models of pain, however, are not unique to this area of research, as they cut across several therapeutic areas. Despite the deficiencies, failures and concerns, existing animal models of pain continue to be of widespread use and are essential to progress in pain research as well as in other areas. Although not focusing on specific animal models of pain, this paper seeks to examine general issues facing the use of these models. It does so by exploring alternative approaches which capture recent developments, which build upon principles and concepts we have learned from Berend's contributions, and which provide the prospect of helping to address the absence of novel therapeutics in this area.

1. Introduction

A great deal of attention has been focused on the 'valley of death' – the significant void in the development of new therapeutics ad the tremendous unmet medical needs that span multiple therapeutic areas. The pressures on pharmaceutical companies to deliver new and innovative compounds in a wide variety of therapeutic areas, coupled to recurring failures in late-stage clinical development, have forced attention on and an evaluation of a large number of potential factors contributing to these failures (Munos and Chin, 2011; Paul et al., 2010; Scannell et al., 2012). The challenges in bringing innovative drugs to patients are often seen to predominate in the area of neuropsychiatric disorders where progress, as noted by the introduction of novel and more effective therapeutics, has been slow over the past half-century. There have been a number of noteworthy failures in bringing new drugs forward to treat disorders such as depression and schizophrenia, conditions where a large percentage of patients are not responsive to current drugs or where these drugs treat only certain components of the disorders. Nestler and Hyman (2010), in addressing these concerns, comment that most of the current drugs used to treat these conditions were 'reverse engineered' from drugs that were discovered over 60 years ago, with most of today's medications consisting of variations on those early clinical discoveries. A major focal point in attempting to address these difficulties has been the recurring concerns surrounding the poor predictive validity of animal models. It is interesting that the prolific development of a wide variety of animal models – or animal assay systems – along with the elucidation of neuropharmacological mechanisms of those drugs *followed* rather than preceded the introduction of clinically effective drugs to treat depression, schizophrenia and anxiety. Although neither the mechanisms of those drugs nor the pathophysiology of the disorders were known at the time, the animal models that were developed as a result of having clinically efficacious drugs aided considerably in unraveling the neuropharmacological mechanisms which were then be used to evaluate newly developed compounds and also led to the identification of the neurochemical bases of these disorders. This general sequence of events also characterizes the use of animals in models

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http://dx.doi.org/10.1016/j.ejphar.2014.11.046
0014-2999/

in pain research which, to a large extent, were developed on the basis of their sensitivity to morphine and other known analgesics. Despite considerable progress in many areas of neuroscience, the paucity of new drugs to treat neuropsychiatric disorders, as well as pain, has drawn heightened attention not just to the lack of new drugs but also to our lack of understanding the pathophysiology of these complex disorders. Although addressing this issue is critically important, it is ironic perhaps that our current understanding of the pathophysiology of these conditions and the neuropharmacological mechanisms associated with those drugs was completely absent when these drugs were introduced. The point is that many of the clinically efficacious drugs used in contemporary psychiatry and pain therapeutics emerged from clinical observations with virtually no understanding of the underlying pathophysiology. Consequently, the inability to break out of the 'vicious circle' where existing animal models may only predict efficacy based on the pharmacological mechanisms on which those models were developed remains a significant challenge. Moreover, it may not be possible to use these drugs as pharmacological tools to probe more deeply into an understanding of the pathophysiology of the conditions for which they are used because they may yield few additional insights to aid in the discovery of new targets and therapeutics.

The historical precedent of discovering clinically efficacious drugs based on clinical observations of 'off target' effects, such as the elation of tuberculosis patients treated with iproniazid that led to the use of tricyclic antidepressants in the 1950s, rather than on the bases of the underlying pathophysiological mechanisms, does not imply that the continued pursuit of mechanisms is not warranted. Extensive research in oncology has yielded a much deeper understanding of the molecular mechanisms and genetic variants of different cancers which, as is the case with many neuropsychiatric and neurological disorders are complex and heterogeneous. In turn, these advances, which have transpired over the past few decades have led to deeper insights into different types of cancer and to therapeutics with greater specificity and enhanced efficacy. A better understanding of the heterogeneous mechanisms in oncology has permitted the identification of novel targets and compounds that can intervene in key steps of tumor progression, including metastatic processes, by targeting the tumor microenvironment (Whitney et al., 2011; Witz, 2009; Jain, 2013). Despite the significant challenges of working on central nervous system disorders, it is essential to acknowledge the need and to vigorously pursue robust scientific efforts directed at a deeper understanding of signaling pathways, molecular targets and genetic idiosyncrasies which have the potential to reveal new approaches to psychiatric and neurological disorders. Although a number of companies have deemphasized programs in neuropsychiatry and pain due to the challenges and difficulties of working in these areas, the complete absence and repeated failure of drugs to treat Alzheimer's disease, stroke, Parkinson's disease and amyotrophic lateral sclerosis indicates that these challenges also extend to neurological disorders. One of the recurring themes that surfaces in portraying the difficulties in drug discovery and development, regardless of the therapeutic focus, is on the use as well as the utility of animal models in pharmacological and neuroscience research. Indeed, multiple disease determinants and inadequate animal models were listed as major problems in neuropsychiatric drug development (Becker and Greig, 2010). Although Nestler and Hyman (2010) have stated that it is difficult to imagine substantial progress in either the understanding of pathophysiology or in the development of new therapeutics without the benefit of good animal models, there is not a clear consensus nor is there a uniformly accepted effort on how to develop newer models that may have more predictive value than those currently in use.

2. Animal models – general issues and challenges

An issue in the development and use of animal models is that of translating what are too often subjective assessments based on those models into objective, reproducible measures of behavior that have predictive veracity and reliability. A number of analyses have been conducted to assess preclinical efficacy studies using animal models and their translational or predictive accuracy (e.g., Hackam, 2007; Henderson et al., 2013; Perel et al., 2007; Tsilidis et al., 2013). The general conclusion of these studies, as well as related and recent commentaries (e.g., Pound et al., 2014), points to a general concern about the difficulty in replicating certain findings, the prevalence of methodological approaches that threaten the validity of preclinical studies and the excess significance bias, specifically in neurological diseases. A number of papers have provided disconcerting testimony to the lack of replicability of many results, the problems of publication bias, as well as bias in interpretation and reporting, together with methodological issues that include inadequate preclinical preparations for clinical trials. These issues further confound the difficulties in using animal models to predict clinical efficacy (Becker and Greig, 2010; Brunner et al., 2012; McGonigle and Ruggeri, 2014). A series of recommendations from these multiple analyses is that there be more uniformity and transparency in reporting the results of animal studies, that authors use a checklist to aid in experimental design and that this information would be submitted along with a manuscript when submitting study results to a journal to aid in the review process. Tsilidis et al. (2013) used a statistical technique to evaluate whether the number of published animals studies with a statistically significant positive effect was too large to be true. These investigators assessed 4445 animal studies for 160 candidate treatments for neurological disorders that included Parkinson's disease, spinal cord injury, and Alzheimer's disease and observed that only 919 of these studies would have been expected to yield a positive result. Only eight of the 160 evaluated treatments should have been subsequently assessed in humans. The finding that there are animal studies reporting too numerous positive results in neurological disorders raises a number of concerns. This point also has been emphasized in pain research in a review by Rice et al. (2008) that found a number of experimental or methodological biases when novel compounds were assessed for efficacy in animal pain models. These biases, concentrating on animal models of neuropathic pain, include the failure to randomize subjects to experimental conditions, to conduct the assessments blinded to the treatments, to provide exposure data to the drug and to report withdrawals and dropouts from the study (see also Berge, 2014). Of additional concern is the frequent mismatch of outcome measures in animal studies with those assessed in clinical trials. For example, in human trials the primary efficacy measure is typically that of spontaneous continuous activity; these assessments typically also include evaluations of physical and emotional function and sleep disturbances but, rarely, are these assessed in animal efficacy studies (Percie du Sert and Rice, 2014). Despite these concerns that surround methodological and procedural issues, animal models are essential for progress in the area of pain research to aid in the elucidation of mechanisms and pathophysiology and to guide the direction of new therapeutic targets and compounds into human clinical evaluation (Mogil et al., 2010). However, in light of the many issues surrounding the use of existing animal models, continued assessment and refinement, together with the development of new models are essential pursuits. Fortunately, there are a number of efforts underway to address some of the fundamental issues as well as to seek closer alignment with clinical conditions and 'backward translation' which, hopefully, might parallel those advances made decades ago in the discovery of psychotherapeutic drugs (see below).

Please cite this article as: Barrett, J.E., The pain of pain: Challenges of animal behavior models. Eur J Pharmacol (2015), http://dx.doi.org/10.1016/j.ejphar.2014.11.046