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Themed Issue: Translational Neuropharmacology – Using Appropriate Animal Models to Guide Clinical Drug Development

EDITORIAL

Translational neuropharmacology and the appropriate and effective use of animal models

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This issue of the *British Journal of Pharmacology* is dedicated to reviews of the major animal models used in neuropharmacology to examine drugs for both neurological and psychiatric conditions. Almost all major conditions are reviewed. In general, regulatory authorities require evidence for the efficacy of novel compounds in appropriate animal models. However, the failure of many compounds in clinical trials following clear demonstration of efficacy in animal models has called into question both the value of the models and the discovery process in general. These matters are expertly reviewed in this issue and proposals for better models outlined. In this editorial, we further suggest that more attention be made to incorporate pharmacokinetic knowledge into the studies (quantitative pharmacology). We also suggest that more attention be made to ensure that full methodological details are published and recommend that journals should be more amenable to publishing negative data. Finally, we propose that new approaches must be used in drug discovery so that preclinical studies become more reflective of the clinical situation, and studies using animal models mimic the anticipated design of studies to be performed in humans, as closely as possible.

LINKED ARTICLES
This article is part of a themed issue on Translational Neuropharmacology. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2011.164.issue-4

Pharmacology is the study of novel chemical entities and drugs, and their interactions with the body. However, it is also a truism that these investigations always have, as an end product, the aim of either producing new medicines or enabling the physician to optimize the use of an existing drug. This goal of wanting to produce new drugs has resulted over the years in phrases such as 'from mouse to man' or 'from bench to bedside' and the British Pharmacological Society strap line 'Today's science; tomorrow's medicine'. The rather recent use of the phrase 'translational pharmacology' highlights this goal in that it emphasizes the steps that have to be taken to move (or translate) basic molecular pharmacological science into a final and fully approved therapeutic agent. That translation almost always involves animal models of disease in order to evaluate the possible therapeutic use of a compound.

The review of Fineberg *et al.* (2011) briefly details the criteria for grouping animal models (predictive validity, construct validity and face validity), as originally proposed by Willner (1984) and refined by Geyer and Markou (1995; 2002). All three types are evaluated expertly and critically by the authors of the articles in this issue as they focus on the different models that are currently being used in the search for better treatments for psychiatric and neurological disorders. Others have recently reviewed the general problems of using animal models in this search (Spedding *et al.*, 2005; Markou *et al.*, 2009) and it is not necessary to repeat here the weaknesses of animal models in the process of identifying novel drugs in neuroscience. Most drugs developed to treat psychiatric disorders were discovered empirically and shown subsequently to be active in animal models. Furthermore, several conditions rely heavily on the assessment of

compounds in a single model, such as occlusion of the middle cerebral artery to model acute ischaemic stroke (Macrae, 2011), experimental allergic encephalomyelitis for examining drugs for multiple sclerosis (Constantinescu *et al.*, 2011) and the spontaneously hypertensive rat for investigating drugs for attention-deficit hyperactivity disorder (Wickens *et al.*, 2011). Such models can only partly replicate the full clinical condition or pathology of the disorder. Other data rely heavily on the predictive value of acute behavioural tests to evaluate the ability of compounds that only work on chronic administration in the disorder, such as the Porsolt test for antidepressants, elevated plus maze for anxiolytics (Cryan and Sweeney, 2011) and prepulse inhibition of acoustic startle for antipsychotics (Jones *et al.*, 2011). The state behaviour evoked in response to a provoking stimulus in such tests may involve different neuronal circuits and neuropharmacology to reproduce trait behaviour seen without a stimulus, which more accurately reflects the pathological condition. Using such high through-put screens with limited construct validity is likely to lead to an unreliable outcome, particularly for disorders where there are currently few reference compounds and no 'gold standard' drug with high therapeutic effect available. Finally, most studies are still focused on better treatments for the symptoms, rather than trying to understand the causal molecular mechanisms and prevent the development of the disorder. The latter developmental approach might provide entirely new therapeutic targets if reliable predictive biomarkers were available, in particular for psychiatric disorders with slow developmental time courses. The lack of success in developing new compounds in this area, particularly those working through novel mechanisms is currently leading to a crisis of confidence in the neuroscience community (particularly the pharmaceutical industry where many companies are terminating in-house research) and is leading to questions about animal models (will their use only allow discovery of more 'me too' drugs?). Better models, particularly those that model ever more closely the clinical pathology, are to be welcomed. However, we feel there are also a couple of simple approaches that may improve the use of animal models.

The first is much better use of pharmacokinetic–pharmacodynamic integration (sometimes called quantitative pharmacology, or PKPD). As we have pointed out elsewhere (Gabrielsson and Green, 2009) this approach is central to drug discovery in the pharmaceutical industry but less practiced in academic laboratories. Basically, it requires bringing into play pharmacokinetic knowledge early in the discovery process as is noted in this issue by Berge (2011). Unless consideration is given to the pharmacokinetics of the drug, including plasma (and sometimes brain) drug concentrations, plasma protein binding, plasma half-life and active metabolites, then accurate extrapolation to clinical use cannot be made (Gabrielsson *et al.*, 2010). We acknowledge this will give difficulty to some academic studies where drug analysis techniques may not be available. However, the experimenter should try to obtain as much information on the pharmacokinetics of the drug as possible when designing the experiment. Otherwise, any experimental data obtained on the effects of the compound are of very limited value, particularly if similar drug exposure cannot be achieved in human subjects.

A second point is that full experimental details should be available in any published article. Investigators often fail to give full details of methodology, sometimes because they feel the method is so well known that some information is 'self evident' and sometimes because journals are very restrictive in space allowed for methods. However, to fully evaluate the quality and reproducibility of a result we need to know that the work was well performed. It is notable that in experimental stroke studies (see Macrae, 2011) even simple information such as the method of blinding of the experimenter to the drug administration and the method of randomization of animal subjects is often missing (Dirnagl and Macleod, 2009). Statistical quality is also a key item and this and other matters relating to proper reporting of animal experiments have recently been outlined (McGrath *et al.*, 2010). There is a related problem regarding reproducibility. In general, and in contrast to many clinical studies, negative studies are not reported. However, such information is vital and can prevent publication bias. Clearly, the problem involves the investigator (many people do not like to publish negative data), the referees, who fail to appreciate the scientific value of publishing negative results, and journal editors who likewise do not wish to use up valuable space with material that is unlikely to be cited. Regardless of the pursuit of scientific rigour and the politics of maintaining a journal's impact factor, from a practical perspective how are we to assess data reproducibility unless we also know when investigators find they fail to replicate the published findings of others? Perhaps journals should have an online repository for negative results.

Even when papers are published that fail to confirm the results of others, explanations are often provided citing probable reasons which include strain differences, different species (and here one can sometimes explain the conflicting information if pharmacokinetic data had been produced) or slightly different methodology (so emphasizing the need for full details to always be published). Oddly, authors of negative findings tend to be required to supply much more substantial justification for their findings in their papers than authors who obtain the 'desired' positive outcome. These problems or 'excuses' bring us to another vital aspect of drug discovery which we feel must now be incorporated into the development process and this is the more extensive use of meta-analysis.

Recently, one of us was involved in what was probably the first meta-analysis which used individual animal data (Bath *et al.*, 2009a). The study evaluated data obtained on a novel neuroprotectant that had been examined in animal models of stroke. The problems that arose, such as lack of information on methodology and slightly different techniques used in the investigations, prompted us to propose that any animal studies being used to decide whether a new drug should be developed for clinical use should be conducted more in the manner by which drugs are examined during Phase III studies (Bath *et al.*, 2009b). It is all too easy to be convinced of the worth of a compound that has been examined repeatedly in uncomplicated studies. By that we mean examining the effect of the drug in young healthy animals rather than more challenging situations such as older animals with co-morbid conditions or the use of dosing regimens that are not feasible in the clinic. An example of the latter situation is giving a potential stroke drug soon after the infarct

rather than 4–6 h later, which is when most patients are likely to present. Multicentre studies would produce data amenable to a meta-analysis. This will, however, require major organization and will be expensive, although such costs will be modest compared with those incurred in a failed clinical trial. This is not to say that scientists may not conduct any individual study they may wish to undertake rather than as part of a coordinated multicentre study, merely that such studies should not be used for the evaluation as to whether a novel drug is to be progressed to clinical trial.

Recently, Enna and Williams (2009) wrote a provocative essay that proposed that part of the problem responsible for the lack of novel clinically efficacious compounds in neuroscience over the last 15 years was the reliance on target identification for the treatment of any disease and the subsequent development of drugs to act at that target. As they stated this approach 'requires a good understanding of target physiology and its integration with the target organ, with a hierarchical integration from *in vitro* cellular and functional tissue studies to animal models that reasonably predict human responses'. As can be seen from perusal of the articles in this issue many drugs used in neuroscience were developed empirically and this does not assist in further drug discovery, other than producing more of the same, unless we have a full understanding of why the beneficial drugs are effective. If we take this argument further then it follows that we should go back and perhaps spend at least some time doing what has been described disparagingly as the 'look see' and 'I wonder if' type of experiment. The problem is the current resistance to hypothesis testing. Currently in basic science in academia and industry you cannot, respectively, either fund or be given time to perform a study until you have enough preliminary data to make performing the investigation almost redundant.

A key aspect of such investigations is the animal model and we must therefore not only choose the best models to conduct such studies, but use multiple models where available to ensure replication of findings. We hope this issue of the *British Journal of Pharmacology* will help investigators to make that informed choice.

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