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Themed Section: Animal Models in Psychiatry Research

EDITORIAL

Found in translation? Commentary on a BJP themed issue about animal models in neuropsychiatry research

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This themed issue of Br J Pharmacol is dedicated to the utility and needs of animal models in psychiatry research. The following articles document strengths and weaknesses, indicate areas where better models are sorely needed and provide examples where pharmacological studies may result in mechanistic breakthrough and aid in drug development. In addition, complicating factors both in disease and treatment strategies are canvassed, such as sex differences, genetic and environmental influences. While not exhaustive, the intention was to use a number of exemplars to stimulate discussion around how animal models can aid in improving our understanding and treatment of many devastating conditions.

LINKED ARTICLES
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Karl Menninger once said 'unrest of spirit is a mark of life', acknowledging the widespread occurrence of psychiatric disorders. According to the World Health Organisation 2014 Global Health Estimates, 'mental and behavioural disorders' make up 7.3% of all disability adjusted life years (DALYs) while 'neurological conditions' add an additional 2.9% of all DALYs. Tellingly, unipolar depression sits within the top 10 of all causes (see http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html). As stated in the 2013 World Health Report 'The creativity and skills of researchers should be used to strengthen investigations not only in academic centres but also in public health programmes, close to the supply of and demand for health services'(WHO, 2013). The ever-growing incidence rates for psychiatric disorders and the need for better therapeutic approaches make this somewhat generalized statement a sobering reality check. Accordingly, we have dedicated a special issue of the *British Journal of Pharmacology* to scrutinize animal models in the psychiatry domain and to provide some direction for the field. Better models with better validity will undoubtedly assist in knowledge advances that may facilitate drug development. One should however recognise that modelling psychiatric disorders with constellations of symptomology and comorbidity is a difficult, often impossible, task. Nevertheless, advances in modeling aspects of disorders are happening and will continue to be refined going forwards.

Parenthood is a time of immense change. In addition to obvious lifestyle changes (and lack of sleep!), there is substantial physiological and behavioural plasticity. The opening review of this issue details numerous manipulations that have been used in an attempt to model aspects of postpartum mood and anxiety disorders (Perani and Slattery, 2014). For example, stress, diet, deliberate hormone fluctuation with phantom pregnancy, separation and selective breeding have all been examined in this regard. As indicated by Perani and Slattery, a major drawback in many of the studies has been a relative lack of end-point readouts and therefore a need going forward is to more broadly characterise the consequences of an individual manipulation. In addition, developing models that incorporate findings from genetic association studies is also clearly warranted.

There is a recent appreciation that adolescence maybe a particularly vulnerable time for the onset of certain psychiatric diseases (O'Connor and Cryan, 2014). As highlighted by Ganella and Kim, anxiety disorders often present in childhood and early adolescence (Ganella and Kim, 2014),

suggesting that early diagnosis and intervention may have long-lasting benefit. Indeed fear learning has clear developmental modulation, as has the 'therapeutic' process of extinction. Interestingly, in juvenile subjects it is suggested that extinction may not involve new learning but rather may be a form of erasure. This would then argue for behavioural therapies in children as soon as possible after diagnosis of an anxiety disorder (Ganella and Kim, 2014). In older subjects, extinction is well-established as an active learning process and is widely studied as a translational behavioural intervention for anxiety. Thus, there is a considerable literature detailing conditioned fear and the extinction of conditioned fear. Here, Bukalo and colleagues provide a review of the pertinent circuitry for extinction of conditioned fear and a wide range of pharmacological intervention strategies (Bukalo *et al.*, 2014). Indeed, they conclude that despite the obvious major challenges that beset all CNS drug development, systems neuroscience advances should ultimately identify molecular targets for new therapeutics. Nevertheless, this should be paralleled by deeper investigation of behavioural approaches which would likely reach patients sooner than a new chemical entity. As with anxiety, depression also presents with cognitive impairment. The issue of cognitive affective biases in depression, and the ability to model these in animals is detailed along with pharmacological validation studies (Hales *et al.*, 2014). While these approaches to depression are in relatively early days, studies to date suggest this as a worthy line of enquiry, potentially enabling causal mechanistic studies as well as playing a part in drug development.

In addition to anxiety disorders, extinction has also been used in the context of addiction research and treatment. Perry and colleagues present a discussion of how cues and contextual stimuli regulate drug use and also relapse (Perry *et al.*, 2014). Indeed, in the case of relapse prevention, they argue how the cues themselves can become treatment targets via active extinction training in a relevant contextual environment. This opens an arena for small molecule drugs to be employed to facilitate the learning process behind cue extinction procedures and thereby strengthen the ongoing protection against relapse. Addiction is a complex, multi-faceted disorder and often shares comorbidity with other psychiatric disorders. The relationship between impulsivity and addiction is addressed by Jupp and Dalley (2014), and examines whether treating impulsivity can also impact upon drug-seeking. Aberrant eating patterns are increasingly likened to addiction disorders due to common psychological and anatomical systems being implicated in both disorders. There are a number of models that recapitulate facets of both binge eating and anorexia nervosa (van Gestel *et al.*, 2014). In both cases, drugs targeting monoamine systems are a major focus of preclinical and clinical investigations.

In 2009, the incidence of eating disorders in the UK was 164.5 per 100,000 girls aged 15–19, almost 10-fold the number for boys of the same age (Micali *et al.*, 2013). This exemplar highlights the need to consider sex when modeling disorders in animals. Indeed the National Institutes of Health in the US have recently unveiled policies to ensure that preclinical research they fund considers females and males in all animal studies (Clayton and Collins 2014). Two reviews address this issue and highlight how sex can interact with genetic, environmental and pharmacological mechanisms in affective disorders (Kokras and Dalla, 2014; Joel and Yankelevitch-Yahav, 2014). Indeed, it is argued that 'sexual dimorphism' should be abandoned and further that 'sex differences' are reconsidered as 'sex interactions' (Joel and Yankelevitch-Yahav, 2014). In a similar manner, McOmish and colleagues address critical issues of face, construct and predictive validity in animal models with the complicating factors of gene x environment interactions that are a feature of our life (McOmish *et al.*, 2014).

As mentioned above, modeling of complex behavioural disorders in animals is fraught with danger. Even if the aetiology of the human condition is known, making a robust animal model can be difficult. Consider then the task of modeling a human condition for which the aetiology is unknown! Migraine is an example of a chronic disorder for which the pathophysiology in humans is still equivocal, yet there are a number of models that have helped our understanding of specific aspects of headache and migraine (Erdener and Dalkara, 2014). Indeed, this demonstrates the need for forward and reverse translation in all animal modelling, where advances in human studies (such as imaging) can be applied to the pertinent models and findings in such models can be tested in human studies.

This special issue began with post-partum disorders and wraps up with a discussion of post-stroke depression (Kronenberg *et al* 2014). Depression is common after stroke, and those who succumb typically show worse outcomes. Evidence is presented to show how in rodent models, fluoxetine and citalopram have shown efficacy not only to reduce post-stroke 'depression' but have also improved other outcomes, such as lesion size and extrafocal degeneration. This is complemented by positive trials of fluoxetine in human stroke patients, irrespective of depression status (Kronenberg *et al* 2014).

This Special Issue therefore provides food for thought regarding conceptualizing and putting into practice animal models that have relevance in psychiatric research and drug development strategies. The purpose was not to cover every disorder, but rather highlight some examples that will hopefully stimulate debate within the field. Research areas that have been relatively neglected to date are particularly focused on. Readers are also referred to a previous Special Issue in the Journal (Green *et al.*, 2011) that focused on other disorders such as schizophrenia, anxiety and Alzheimer's Disease (Jones *et al.*, 2011; Cryan & Sweeney, 2011, Van Dam and De Deyn, 2011). A major challenge going forwards is to not only incorporate new technologies and methodologies, but to constantly update and back/forward translate when appropriate. Insodoing, this approach may help us to further identify the cause(s) and possible treatments of many debilitating conditions.

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