Please cite this article in press as: Logan RW, McCLUNG CA. Animal models of bipolar mania: The past, present and future. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.08.041

Neuroscience xxx (2015) xxx–xxx

REVIEW

ANIMAL MODELS OF BIPOLAR MANIA: THE PAST, PRESENT AND FUTURE

R. W. LOGAN AND C. A. McCLUNG*

University of Pittsburgh School of Medicine, Department of Psychiatry, 450 Technology Drive, Suite 223, Pittsburgh, PA 15219, United States

Abstract—Bipolar disorder (BD) is the sixth leading cause of disability in the world according to the World Health Organization and affects nearly six million (~2.5% of the population) adults in the United State alone each year. BD is primarily characterized by mood cycling of depressive (e.g., helplessness, reduced energy and activity, and anhedonia) and manic (e.g., increased energy and hyperactivity, reduced need for sleep, impulsivity, reduced anxiety and depression), episodes. The following review describes several animal models of bipolar mania with a focus on more recent findings using genetically modified mice, including several with the potential of investigating the mechanisms underlying 'mood' cycling (or behavioral switching in rodents). We discuss whether each of these models satisfy criteria of validity (i.e., face, predictive, and construct), while highlighting their strengths and limitations. Animal models are helping to address critical questions related to pathophysiology of bipolar mania, in an effort to more clearly define necessary targets of first-line medications, lithium and valproic acid, and to discover novel mechanisms with the hope of developing more effective therapeutics. Future studies will leverage new technologies and strategies for integrating animal and human data to reveal important insights into the etiology, pathophysiology, and treatment of BD.

This article is part of a Special Issue entitled: Neuropsychiatric Disease. **© 2015 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: bipolar disorder, animal models, mania, circadian rhythms, genetics, mood stabilizers.

Contents

INTRODUCTION

Bipolar disorder (BD) is a complex disease defined by periods of both mania and depression with euthymic or normal mood states between episodes. Manic episodes can consist of hyperactivity, elevated mood or agitation, racing thoughts, reckless behavior, little need for sleep, and sometimes psychosis. Depressive episodes as defined by the DSM V can include persistent sadness, fatigue, eating disturbances, sleep disturbances, suicidal thoughts, guilt and social withdrawal. The cause of BD is unknown and may involve both genetic and environmental factors (Shinozaki and Potash, 2014). The mood-stabilizing therapeutic effects of lithium (a salt) and valproate (an anticonvulsant) were discovered by accident and in the absence of any significant mechanistic understanding of BD (Can et al., 2014). While current

*Corresponding author. Tel: +1-(412)-624-5547; fax: +1-(412)-624-5280.
E-mail address: mcclungca@upmc.edu (C. A. McClung).

Abbreviations: AMP, amphetamine; AMPT, alpha-methyl-p-tyrosine; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BPM, behavioral pattern monitor; CDP, chlordiazepoxide; CRF, corticotropin release factor; EEG, electroencephalography; GCLM, Glutamate-cysteine ligase modifier ; GSH, glutathione; GSK-3, glycogen synthase kinase-3; IGT, Iowa Gambling Task; NAc, nucleus accumbens; PKC, protein kinase C; PPI, paired-pulse inhibition; PV, parvalbumin; VPA, valproic acid.

http://dx.doi.org/10.1016/j.neuroscience.2015.08.041
0306-4522/

treatments are generally effective for the reversal of manic episodes and preventing future episodes, these medications have limited, if any, efficacy on their own in the acute treatment of depressive episodes (McInerney and Kennedy, 2014). Moreover, standard antidepressant medications used either as monotherapies, or in conjunction with mood stabilizers or antipsychotics, are generally ineffective for treating depressive episodes, and may induce mood switching in a subset of patients with rapid cycling BD (De Wilde and Doogan, 1982; Himmelhoch et al., 1982; Gijsman et al., 2004; Amsterdam and Shults, 2005; Sachs et al., 2007; McElroy et al., 2010; Sidor and Macqueen, 2011; McInerney and Kennedy, 2014). Although there are a few studies suggesting therapeutic efficacy of antidepressant monotherapy for bipolar depression, current recommendations indicate antidepressants be used only in combination with mood stabilizers if those first-line medications fail (McInerney and Kennedy, 2014). Despite their effectiveness in the treatment of mania, chronic treatment with current mood-stabilizing drugs often results in serious side effects that make patient compliance difficult and burdensome. Our understanding of the etiological mechanisms of BD is poor. Therefore, the use of appropriate animal models should ultimately aid in the development of novel, potentially more efficacious treatments for this complex disorder.

The screening of compound libraries in animal models could also prove fruitful in the search for new medications. Most of the early mechanistic studies of BD in animals have focused on changes that occur following the administration of lithium or other agents often on animals that are comparatively "normal", which may limit the interpretability and applicability of these studies since lithium has very little effect on healthy individuals while having therapeutic effects on those suffering from mania (Calil et al., 1990). Therefore the changes in the brain that occur in wild-type rodents may not represent the same changes that occur in a rodent displaying mania-like behavior.

EVALUATING ANIMAL MODELS OF BD: ISSUES OF FACE, PREDICTIVE, AND CONSTRUCT VALIDITY

The use of rodent models that cut across multiple types of validity is vitally important to our understanding of psychiatric diseases and the search for better treatments. Face validity refers to the extent to which an animal model recapitulates important features of the human disease, such as neuroanatomical, biochemical, and/or behavioral phenotypes. There are few, if any, neurobiological pathologies that are known, with any certainty, to be biomarkers of the psychiatric disease. Even single behaviors may not completely map onto the clinical symptomology they are intended to model, especially when considering diagnoses are 'inaccurate' and 'imprecise' due to poor diagnostic criteria. Face validity is typically considered to be the requirement for reasonable 'symptomatic' homology or overlap with diagnostic criteria. This could pose a problem when diagnostic criteria are poorly defined or based solely on phenomenology (Chesler and Logan, 2012). Another issue arises when adhering to strict definitions of face validity—excessive anthropomorphization of rodent behavior. Most, if not all, of the animal models discussed here recapitulate at least one, but usually several, of the core behavioral phenotypes of bipolar mania, such as reduced depression, and increased impulsivity, or risk-taking behaviors. Face validity means also recapitulating anatomical, biochemical, or neuropathological features of the disease. Another form of this is sometimes referred to as pathological validity, whereby animal models recapitulate observed postmortem pathology from brains or other tissues found in the human disease. Human postmortem studies, along with the advent of newer technologies to derive neurons from pluripotent stem cells collected from patients with disease, should provide a clearer understanding of the mechanisms involved in the pathophysiology of BD.

Construct validity is the degree to which a test measures what it claims to measure. It often refers to the relevance or translational nature of the methods by which a model is constructed. This might be achieved by exposing an animal to an environmental risk factor,

Table 1. Modeling human bipolar mania in rodents

Behavioral endophenotype	Rodent paradigm
Reduced anxiety, increased novel exploration	Elevated plus maze; dark–light box; open field arena; social interaction test, novelty-suppressed feeding
Reduced depression	Forced swim test, tail suspension test, learned helplessness test
Impaired sensory processing	Paired-pulse inhibition (PPI)—sensorimotor gating*
Risk-taking behavior	Iowa Gambling Task (IGT)*
Impulsivity	IGT*
Impaired decision-making	IGT*
Psychostimulant-induced hyperactivity	Cocaine or amphetamine injection, repeated injections for locomotor sensitization
Hedonia	Sucrose preference; cocaine or amphetamine self-administration*; intracranial self-stimulation (ICSS) of medial forebrain bundle; two-bottle free-choice alcohol drinking; cocaine-conditioned place preference (CPP)
Hyperactivity	Open field arena; homecage monitors; wheel-running; behavioral pattern monitor (BPM)*
Increased sexual activity	Mounts, intermission, and ejaculation events
Increased goal-directed	BPM*
Repetitive movements	BPM*
Aggressive behavior	Resident–intruder test
Reduced or disrupted sleep	EEG; circadian activity; sleep–wake monitoring*
Disrupted circadian rhythms	Circadian wheel-running activity; temporal patterns of behavior

* Demonstrated direct translational relevance to human bipolar disorder.

Please cite this article in press as: Logan RW, McCLUNG CA. Animal models of bipolar mania: The past, present and future. Neuroscience (2015), http://dx.doi.org/10.1016/j.neuroscience.2015.08.041