Neuroscience 321 (2016) 189–196

REVIEW

ANIMAL MODELS OF RECURRENT OR BIPOLAR DEPRESSION

T. KATO,* T. KASAHARA, M. KUBOTA-SAKASHITA, T. M. KATO AND K. NAKAJIMA

Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Brain Science Institute, Japan

Abstract—Animal models of mental disorders should ideally have construct, face, and predictive validity, but current animal models do not always satisfy these validity criteria. Additionally, animal models of depression rely mainly on stress-induced behavioral changes. These stress-induced models have limited validity, because stress is not a risk factor specific to depression, and the models do not recapitulate the recurrent and spontaneous nature of depressive episodes. Although animal models exhibiting recurrent depressive episodes or bipolar depression have not yet been established, several researchers are trying to generate such animals by modeling clinical risk factors as well as by manipulating a specific neural circuit using emerging techniques.

This article is part of a Special Issue entitled: Neuropsychiatric Disease.

Key words: depressive disorder, bipolar disorder, model mice.

Contents

*Corresponding author. Address: Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Brain Science Institute, Hirosawa 2-1, Wako, Saitama 351-0198, Japan. Tel: +81-48-467-6949; fax: +81-48-467-6947.
E-mail address: kato@brain.riken.jp (T. Kato).

Abbreviations: ADHD, attention deficit/hyperactivity disorder; DICE-K, doxycycline-inhibited circuit-exocytosis knockdown; DREADD, designer receptors exclusively activated by designer drugs; DRN, dorsal raphe nucleus; mPFC, medial prefrontal cortex; OB, olfactory bulbectomized; RDoC, Research Domain Criteria; VTA, ventral tegmental area.

INTRODUCTION

Depression imposes a large social burden due to substantial impairment and disability in everyday activities at work, school, and home; the limited efficacy of existing treatments; and a high rate of lifetime prevalence. Depression is also a risk factor for somatic diseases such as cardiovascular disease (Lin et al., 2014), and maternal depression has been shown to affect child development (Ohoka et al., 2014).

Approximately 16% of patients seeking treatment for a major depressive episode have bipolar disorder (Angst et al., 2011). Bipolar disorder is characterized by recurrent depressive and (hypo)manic episodes. The course of bipolar disorder is dominated by the depressive state (Judd et al., 2002, 2003). Though bipolar depression is associated with characteristic features such as early onset, psychotic symptoms, hypersomnia, and hyperphagia (Mitchell et al., 2008), there is no "point of rarity" between depressive states of unipolar depression and bipolar disorder.

All the currently available antidepressants share a fundamental mechanism of action, i.e., the modulation of monoaminergic neurotransmission (Berton and Nestler, 2006). Studies concerned with the development of new antidepressants with novel mechanisms of action have had limited success. This may be partly due to the lack of adequate animal models of depression and less knowledge about the disease mechanism, which are almost two sides of the same coin.

Although antidepressants were developed to ameliorate the symptoms of acute depression and approved based on this efficacy (Inada and Inagaki, 2015), they are also prescribed to prevent relapses (Piek et al., 2014). Almost half of the patients that recover from major depressive episodes experience relapse (Belsher and Costello, 1988).

Several drugs, such as lithium, lamotrigine, olanzapine, quetiapine, and aripiprazole, are known to have preventive effects for bipolar disorder (Kanba et al., 2013), some of which might also be effective for unipolar depression (Zhou et al., 2015). However, none of these drugs were developed specifically for bipolar

http://dx.doi.org/10.1016/j.neuroscience.2015.08.016

disorder; they were developed for schizophrenia or epilepsy with their uses extended to the treatment of bipolar disorder.

This lack of novel treatment specifically designed for the prevention of mood episodes in recurrent depression and bipolar disorder is due at least in part to the lack of animal models exhibiting spontaneous episodes of depression and/or mania. The development of new animal models exhibiting recurrent spontaneous mood episodes is therefore indispensable for the development of new drugs that are effective in the prevention of mood episodes.

In this article, the issues surrounding animal models of recurrent or bipolar depression are discussed.

CAN MOOD DISORDERS BE MODELED BY ANIMALS?

An animal model of mental disorder should ideally satisfy three validity criteria: construct, face, and predictive validity (Kato et al., 2007; Nestler and Hyman, 2010). In reality, most researchers utilize models that satisfy only a subset of these three criteria.

Construct validity

Construct validity refers to how the mechanism of a disease is shared between a disease and the model. Recurrent depression and bipolar disorder are widely thought to be caused by gene-environment interactions. One ideal animal model would be genetically modified animals carrying a genetic mutation that confers a strong risk of a disease with high penetrance. However, research has yet to identify the genes that exert a strong effect on recurrent depression and bipolar disorder (Kato, 2015), and many patients do not have such mutations with strong effects. Thus, the other ideal model would be an animal model that is created by gene-environment interaction, in which a genetic model of a common polymorphism is exposed to an environmental risk factor interacting with the polymorphism.

Among environmental factors, perinatal infection (Parboosing et al., 2013), maternal smoking during pregnancy (Talati et al., 2013), and perinatal complications are established risk factors for bipolar disorder, but also apply to schizophrenia (Schmitt et al., 2014). Childhood maltreatment also is a common risk factor for depression and bipolar disorder (Daruy-Filho et al., 2011) as well as other mental disorders, such as personality and anxiety disorders.

Psychosocial stress is a risk factor for depressive episodes, and is frequently used in animal models, despite the fact that it is common to both mental disorders and general medical illnesses. For example, social defeat stress, which is currently widely used as an animal model for depression in neuroscience research (Tsankova et al., 2006), was initially developed for the study of hypertension (Henry et al., 1967). Additionally, the learned helplessness model, which is frequently used in the study of depression, is also used for the study of gastric ulcers (Pare and Redei, 1993). When stress-induced animal models are used for depression research, the confounding effects of somatic factors should also be considered.

Thus, as discussed above, many of the current animal models rely on limited construct validity.

Face validity

Face validity refers to how the signs and symptoms in animal models are similar to the disease. In clinical settings, recurrent depression and bipolar disorder are defined by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) criteria (American Psychiatric Association, 2013). The DSM-5 criteria for depressive and manic episodes contain several items that rely solely on subjective experience. These include ‘‘depressed mood,’’ ‘‘feelings of worthlessness,’’ and ‘‘thoughts of death’’ for major depressive episodes, and ‘‘elevated mood,’’ ‘‘increased self-esteem,’’ and ‘‘flight of ideas’’ for manic episodes. Therefore, face validity is perhaps more difficult to attain in animal models than the other mentioned criteria. Nonetheless, it should be noted that certain symptoms of depressive and manic episodes, such as sleep disturbances, appetite changes, and agitation/retardation can be reasonably defined, even in animals, by means of behavioral or physiological measurements. For example, sleep disturbances have been detected by electroencephalography (Moreau et al., 1995), and increases in food cravings have been detected by the progressive ratio operant procedure (Willner et al., 1998) in the chronic mild stress model. We used a behavioral test battery to assess the behavioral phenotype of *Wfs1* knockout mice, a possible animal model of depression, and found that the mice showed an increased latency to movement in the passive avoidance test and a longer escape latency in the Morris water maze task in spite that there was no difference of the distance traveled. We interpreted these findings as reflective of psychomotor retardation, that is, slow voluntary movement (Kato et al., 2008). Therefore, we should examine whether an animal model meets the clinical criteria for depression or mania as far as possible. Needless to say, there are fundamental differences in behavioral characteristics between humans and other animals. For example, humans are diurnal whereas many animals used as animal models are nocturnal. These behavioral differences between species should be taken into consideration.

In addition to modeling the symptoms of depression and mania, it is important to model the clinical course of these diseases. In the DSM-5 criteria, major depressive disorder, recurrent, and bipolar I (or II) disorder are defined by characteristic clinical courses that consist of combinations of major depressive and/or (hypo)manic episodes.

DSM-5 is defined by signs and symptoms that either a physician can observe or a patient experiences. Recently, the National Institute of Mental Health of the United States has started to use Research Domain Criteria (RDoC) instead of DSM-5 criteria for research purposes (Casey et al., 2013). RDoC defines mental disorder by behavioral and neurobiological measures on five domains: Negative Valence Systems, Positive Valence Systems, Cognitive