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Partial Rodent Genetic Models for Bipolar Disorder

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Abstract

Bipolar disorder (BPD) is a complex clinical phenomenon. This episodic illness comprises at least four features/components: depression, mania, vulnerability to mood swings in euthymic BPD patients, and spontaneous cyclicity in at least some BPD patients. Currently, there is no rodent genetic model capable of encompassing the whole phenotype of BPD exists; however, recent genetic-behavioral studies have delineated partial models for some components of BPD, namely, depression, mania, and vulnerability or resilience to mood swings. p11 knockout (KO), vesicular monoamine transporter 2 (VMAT2) heterozygous KO, and neural cell adhesion molecule (NCAM) KO mice display anhedonia-like symptoms, and treatment with antidepressants rescues this anhedonia-related phenotype. Mutant CLOCK, glutamate receptor 6 (GluR6) KO, and extracellular signal-regulated kinase 1 (ERK1) KO mice exhibit mania-like behavioral clusters referred to as excessive behavioral excitement; at least some of the exhibited behaviors can be rescued through treatment with mood stabilizers or atypical antipsychotics. Neuronal glucocorticoid receptor (GR) overexpressing, B-cell lymphoma 2 (Bcl-2) heterozygous KO, and Bcl-2-associated athanogene (BAG1) heterozygous KO mice show vulnerability to mood swings. In contrast, neuronal BAG1 overexpressing mice display resilience to mood swings. These mutant mouse strains and the behavioral approaches used to characterize these strains offer an emerging set of research tools for the comprehensive understanding of various components of BPD, and the interrelation of these components at the molecular, cellular, and neuronal circuitry levels. These partial genetic models can also be used as complementary tools to augment other existing behavioral tests and paradigms in drug development for BPD.

Keywords

Bipolar disorder; Mania; Depression; Antidepressants; Mood stabilizers; p11; Vesicular monoamine transporter 2 (VMAT2); Neural cell adhesion molecule (NCAM); Extracellular signal-regulated kinase (ERK); Glutamate receptor 6 (GluR6); Glucocorticoid receptor (GR); B-cell lymphoma 2 (Bcl-2); Bcl-2 associated athanogene (BAG1)

1 Introduction

Animal models are essential for studying the molecular, cellular, and neuronal circuitry mechanisms underlying behaviors or behavioral clusters related to human neuropsychiatric diseases (Berton and Nestler 2006; Crawley 2008; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002). Indeed, such models are pivotal for investigating the therapeutic mechanisms underlying existing treatments, and for evaluating the efficacy of novel therapeutics. With regard to bipolar disorder (BPD), any model expected to capture the whole of the disease would require the following: (1) the animal would be biologically modeled to carry multiple gene alterations implicated by human genetic studies; (2) the behavioral displays of the model animals would cover multiple components of clinical phenomena associated with BPD; and (3) the behavioral alterations exhibited by the model animals would be at least partially responsive to chronic treatments with existing clinically effective antidepressants or mood stabilizers. These three aspects of model animals are often referred to in the literature as constructive, face, and predictive validity (Berton and Nestler 2006; Crawley 2008; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002). While animal models do exist that encompass facets of either depression or mania, to date no animal model of BPD encompassing the cyclic nature of its symptoms has been developed.

For the purposes of behavioral simulation and mechanistic studies, the clinical course and phenomena associated with BPD (Belmaker 2004; Goodwin and Jamison 2007) can be summarized into four components or features: depressive episode, manic episode, spontaneous mood swing or cyclicity, and vulnerability to triggerable/inducible mood changes in euthymic patients. The features of each component and the animal behavioral tests and paradigms to monitor these features will be discussed later.

Mood stabilizers are the treatment of choice for BPD and, although far from perfect, they are generally effective treatments for bipolar depression, mania, or mixed episodes, and are also used to prevent the recurrence of mood episodes (Belmaker 2004; Goodwin and Jamison 2007). Antidepressants are used in conjunction with mood stabilizers to treat bipolar depression; however, when used alone they carry the risk of cycle acceleration or agitation/dysphoria for some patients. With regard to animal models, a collection of antidepressant-sensitive and mood stabilizer (especially lithium)-sensitive behavioral tests are well documented in the literature (for reviews see Berton and Nestler 2006; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002). Some of these tests have been used

to assess whether genetically altered animals display cross-species phenocopies of behavioral facets of BPD.

The term “cross-species phenocopy”, used throughout this chapter and in other related articles, refers to the apparent phenotypical similarity between behavioral displays in model animals and simulated clinical symptoms or syndromes, regardless of the underlying biological causes (Shaltiel et al. 2008). Using this term acknowledges that, despite the behavioral similarity between model animals and human patients, the biological causes of such symptoms in model animals may or may not be similar. Unlike neurological disorders that cause seizures, movement abnormalities, or learning and memory difficulties, mood disorders (BPD or major depressive disorder (MDD)) affect a patient’s subjective feelings or mood, which are the core symptoms of the illness and required for making a diagnosis. This core symptom, obviously, cannot be directly assessed in rodents. Thus, to reflect the limitations associated with animal models, terms, such as “manic mouse” or “depressed mouse” are avoided in the research literature; instead the terms “mania-like behaviors” or “depression-like behaviors,” or “model for mania or depression” are used to highlight the fact that the behaviors of model animals phenocopy the observable diagnostic symptoms or behavioral displays related to mood alterations. The similarity or relevance of the phenocopied behaviors to human mood episodes are further validated, at least in most cases, by noting whether the animal behaviors respond to chronic treatment with antidepressants or mood stabilizers.

Over the years, several genetic mutant mouse strains have been examined using batteries of tests to assess the behavioral components of BPD. These mutant mice carry changes in selected genes previously implicated in mood disorders by human genetic and postmortem studies, or by animal studies on the neurochemical actions of antidepressants and mood stabilizers. Although none of the strains display a phenocopy covering all components of BPD, the data clearly demonstrate that altering these genes in turn alters behaviors related to BPD. Thus, these strains can be considered practical choices for in-depth mechanistic studies of depression or mania as well as of vulnerability to mood swings; they are also useful for evaluating novel therapeutics in conjunction with other widely used animal paradigms assessing antidepressant- or mood stabilizer-sensitive behaviors. In humans, mood disorders manifest as a clinical syndrome. The symptoms of the syndromes are less specific and the same symptom can be present in different illnesses. The major advantage of using genetically altered animals is that mutant animals allow investigators to study behaviors as a cluster, not just the individual acts. Some of the most useful strains for investigating BPD will be discussed in this chapter.

2 Partial Models for Anhedonia and Depression (Table 1)

Depressed or irritable mood and anhedonia are the core symptoms of depression and unequivocally important for clinically diagnosing major depression (American Psychiatric Association 1997). Clinical anhedonia is defined as “markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)” (American Psychiatric Association 1997). According to this definition, one simple way to monitor cross-species

phenocopies of anhedonic displays in rodents is to observe the animals' activity over a specific period of time in either their enriched (e.g. equipped with play objects) or their regular home cages. However, a home cage activity study requires special animal holding facilities or cabinets, video tracking systems, and sophisticated computer software. These are not widely available to the research community. Alternatives do, however, exist. For instance, rodents love to run on the wheel. Indeed, wheel running, like psychostimulants, can induce conditional place preference (Lett et al. 2000), cause cross-tolerance to the rewarding effects of morphine (Lett et al. 2002), and stimulate deltaFosB expression in the reward pathway (Werme et al. 2002). Therefore, home cage wheel running can be used as part of hedonic-like activity measures (Engel et al. 2009).

Another behavior that can be monitored is that of food consumption. Rodents prefer to consume palatable food. As a result, the sweetened solution preference (vs. water) test has been widely used to examine anhedonia-like displays in rodents, although the test protocols vary from study to study. Chronic behavioral stress gradually reduces sweetened solution preference and this reduction can be prevented or reversed through treatment with antidepressants during the course of the stress (Willner 1997). Sucrose, sucralose (a noncaloric sweetener), or saccharin (a more potent noncaloric sweetener) are used to make the sweetened solution for the test. The TRPM5 (transient receptor potential cation channel, subfamily M, member 5) is expressed in taste receptor cells and is essential for sweet, bitter, and amino acid taste signaling. In a study conducted using both wild-type and TRPM5 knockout (KO) mice, de Araujo and colleagues found that both sucrose and sucralose induced consumption preference and activation of the dopamine-nucleus accumbens (NAc) reward system, and that sucrose, but not sucralose, induced similar effects in TRPM5 KO mice (de Araujo et al. 2008). The interpretation of this and other supporting data in their study suggest that overall food reward is mediated through two independent pathways: one relating to calorie-independent palatability initiated in the taste cells, and the other relating to taste-independent caloric load that bypasses the taste cells (de Araujo et al. 2008). In light of the findings from this study, the selection of sweeteners for the preference test should consider the reward-delivering pathways to be monitored.

Another option concerns the fact that rodents spend more time sniffing urine from the opposite sex than either water or novel odors. The female urine sniffing test (FUST) is a novel method for monitoring sexually related hedonic activity in rodents (Malkesman et al. 2009). In this test, water and female urine were presented to male rodents; the animals spent much longer sniffing female urine. While sniffing female urine, males also emitted ultrasonic vocalizations, and had significantly elevated dopamine levels in the NAc. In addition, mice that developed helplessness in the learned helplessness paradigm spent less time sniffing female urine, and treatment with antidepressants rescued these changes.

Nevertheless, the issue of appropriately defining an anhedonia-like phenotype in rodents is an issue that has yet to be resolved. Given that in humans the impact of anhedonia is sustained and spreads into broad aspects of patients' daily activity, and that in rodents each behavioral test has its limitations and confounding factors, one operational definition of an anhedonia-like phenotype in rodents is as follows: experimental animals display concurrent reductions in multiple activities that are known to be preferred by appropriate control

animals, and these reductions cannot be explained by a single or few causes alone, such as locomotive dysfunction, lack of explorative curiosity or neophobia, specific sensory alterations, low sexual drive, or loss of appetite. Thus, anhedonia-like behaviors should be evaluated as a behavioral cluster or pattern rather than a specific act in any given context.

Phenocopies of some other diagnostic symptoms of major depression can also be monitored in rodents. For instance, changes in body weight or appetite can be monitored. Home cage monitoring or tests such as the open field test can be used to evaluate psychomotor agitation or retardation. Home cage monitoring over a 24-h period can also be used to detect sleep disturbances (e.g., insomnia or hypersomnia). Similarly, fatigue or loss of energy can be evaluated using home cage activity, the open field, forced swim, and tail suspension tests, or treadmill running. However, tests to assess behaviors related to diminished ability to think or concentrate, or indecisiveness, need to be developed or adapted from other fields, refined, and validated for use in depression studies. Obviously, it would be very challenging to define and monitor displays related to low self-esteem or hopelessness. Some behavioral paradigms are thought to monitor behavioral despair (e.g., the forced swim or tail suspension tests and the learned helplessness paradigm). However, the link between rodent performance on these tests and the subjective human symptoms of depression for instance, low self-esteem or hopelessness require further examination.

Because no consensus has to date been established regarding how to define genetic models for depression or anhedonia, most investigators use a few behavioral tests, but not the comprehensive evaluation approach suggested above. Given the importance of anhedonia in diagnosing depression in humans, we here focus on those modeling anhedonia in mice.

p11 (also known as S100A10) is a member of the S100 calcium effector proteins (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). In the brain, p11 mediates receptor trafficking (such as 5HTR1B and 5HTR4) as well as ion channels to the cell surface (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). p11 also mediates the behavioral effects of antidepressants and antidepressant-like effects of a selective 5-HTR4 partial agonist (RS67333) on immobility in the tail suspension test and on thigmotaxis in the open field test (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). A postmortem study revealed reduced p11 mRNA levels in multiple brain regions in suicide victims (Anisman et al. 2008). Interestingly, naïve p11 KO mice displayed increased immobility and thigmotaxis as well as reduced consumption of sucrose solution (Svenningsson et al. 2006). These results suggest that p11 KO mice may serve as a genetic model for depression with anhedonic features; this putative model is worthy of further characterization via additional tests and agents such as mood stabilizers and ketamine used to treat depression.

SLC18A2 (solute carrier family 18 (vesicular monoamine), member 2) encodes proteins and is also known as vesicular monoamine transporter 2 (VMAT2), transporting cytosolic monoamines into synaptic vesicles (Christiansen et al. 2007; Fukui et al. 2007). Treatment with reserpine, an irreversible VMAT inhibitor, depletes vesicular monoamine stores and precipitates depression in susceptible individuals (Christiansen et al. 2007; Fukui et al. 2007). A haplotype of VMAT2 has been found to be significantly associated with depressive symptoms in elderly men (Christiansen et al. 2007). VMAT2 heterozygous (HET) KO mice

were hypoactive in the open field test and displayed increased immobility in the forced swim and tail suspension tests (Fukui et al. 2007). Treatment with antidepressants reduced the immobility of VMAT2 HET KO mice. The mice also showed less preference for sweetened but not quinine solutions (Fukui et al. 2007). Thus, VMAT2 HET KO mice are another potential genetic model for depression with anhedonic features, and are worthy of further characterization.

Neural cell adhesion molecule (NCAM, also known as the cluster of differentiation (CD56)) is a cell surface homophilic binding glycoprotein involved in cell cell adhesion. It has been implicated in signaling of growth factor receptors, such as fibroblast growth factor receptor (FGFR) and tyrosine receptor kinase B (TrkB, also known as neurotrophic tyrosine kinase, receptor, type 2 (NTRK2)), long-term potentiation (LTP), long-term depression (LTD), and learning and memory. An early study showed that soluble NCAM was increased in the CSF of depressed patients (Jorgensen 1988), and more recently a genetic study suggested that NCAM polymorphisms confer BPD risk (Arai et al. 2004). Furthermore, behavioral stress and treatment with antidepressants alter NCAM levels in the brain [for a review see Sandi and Bisaz (2007)]. Taken together, these data suggest that NCAM plays a role in mood regulation. There are three main NCAM isoforms resulting from alternative splicing of a single gene. Mice lacking all NCAM isoforms displayed increased immobility in the tail suspension test and reduced sucrose preference (Aonurm-Helm et al. 2008). Treatment with the antidepressants, citalopram and amitripty-line, rescued these phenotypes (Aonurm-Helm et al. 2008), suggesting that NCAM null mice are another potential genetic model for depression with anhedonic features.

3 Partial Models for Mania and Excessive Behavioral Excitement (Table 2)

Manic episodes are characterized by type of mood symptoms (either euphoric or irritable), thought processes (flight of ideas or racing thoughts) and content (inflated self-esteem or grandiosity), attention (distractibility), sleep (less need for sleep), and behavior (more talkative than usual or pressure to keep talking, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences) (American Psychiatric Association 1997; Belmaker 2004; Goodwin and Jamison 2007). For behavioral research purposes, attention, sleep, and behavioral impairments can be summarized in a phenotype known as excessive behavioral excitement (Engel et al. 2009; Shaltiel et al. 2008).

Although it seems model-able in rodents, no definitive test for assessing distractibility in a mania-related phenotype has yet been established. Nevertheless, sleep changes can be monitored through home cage observation, and several tests are suitable for monitoring cross-species phenocopies of “increase in goal-directed activity or psychomotor agitation”. These include tests for open field activity, object exploration, social interaction, resident intruder interaction, sexual activity, female urine sniffing, forced swim, sweetened solution preference, and home cage wheel running. There are also well-documented tests for measuring anxiety-like behaviors, such as center activity in the open field test, the elevated plus maze or zero maze test, the light/dark box, reward/aversion tests, and novelty-induced hypophagia. Recent data suggest that these tests are sensitive enough to measure anxiolytic-

like phenotypes in mutant mice, and that this phenotype can be rescued by treatment with mood stabilizers. Given that mood stabilizers do not produce anxiogenic effects in humans or anxiogenic-like effects in wild-type mice, the effects of mood stabilizers on anxiolytic-like phenotypes in mutant mice suggest that these tests may be useful in assessing risk-taking behaviors. Furthermore, combining the results of this battery of tests helps define the excessive behavioral excitement phenotype in rodents. One suggested definition of this phenotype is that the animal displays most, if not all, of these alterations, is hyperactive in multiple tests, displays increased goal-directed behavior in multiple tests or settings, displays increased risk-taking behaviors in multiple tests or settings, requires less rest or sleep in the home cage, and is distractible. The relevance of the excessive behavioral excitement phenotype to mania can be further validated by examining the response of this phenotype to treatment with mood stabilizers.

One partial genetic partial model for excessive behavioral excitement and mania is mutant CLOCK (mCLOCK) mice. CLOCK is a key component in the molecular circadian machine. Expression of CLOCK and other components of the circadian machine are not restricted to the suprachiasmatic nucleus, suggesting these proteins have broad functions (McClung 2007). These proteins have been implicated in the pathogenesis, pathophysiology, and therapeutic mechanisms of BPD in human genetic and postmortem studies and in animal studies [for a review see McClung (2007)]. mCLOCK mice carry a point mutation that causes protein inactivation (McClung et al. 2005). Research showed that these mice were hyperactive and more responsive to cocaine in both behavioral sensitization and conditioned place preference tests (McClung et al. 2005). Further studies revealed that the mice exhibited increased goal-directed activity, including reduced immobility in the forced swim test, disproportional increase in sucrose solution consumption in the sucrose preference test, and increased number of escapes in the learned helplessness paradigm (Roybal et al. 2007). The mice also displayed risk-taking behaviors, including increased activity in the center of an open field and in the open arms of an elevated plus maze, and reduced latency to approach crackers in a novel cage, even in the presence of bobcat urine. Lithium treatment rescued some of these behaviors, including altered immobility and risk taking in the open field and elevated plus maze tests. The data strongly support that mCLOCK mice may be a valid genetic model for mania and excessive behavioral excitement.

One proposed model for simulating the pathogenesis of mania involves the paradigm of repeated psychostimulant administration, which induces behavioral sensitization (Post 1992). Treatment with lithium partially attenuated the development of cocaine-induced behavioral sensitization (Post et al. 1984). Repeated, but not acute, administration of cocaine attenuated mRNA levels of glutamate receptor 6 (GluR6, also known as glutamate receptor, ionotropic, kainate 2 (GRIK2)) in striatum and cortex (Izawa et al. 2006).

mRNA levels of GluR6 were found to be lower in the postmortem entorhinal cortical tissue of individuals with BPD (Beneyto et al. 2007). The human GRIK2 gene is on 6q16.3 q21, a known “hot spot” for BPD risk genes implicated by linkage studies (Shaltiel et al. 2008). A recent preliminary study suggests that single nucleotide polymorphisms (SNPs) of GRIK2 confer risk for BPD (Shaltiel et al. 2008). Given these indications of constructive validity, the phenotype of GluR6 KO mice was characterized (Malkesman et al. 2009; Shaltiel et al.

2008). These mice were found to be hyperactive on multiple tests, and displayed increased goal-directed behaviors in the forced swim, saccharine preference, female urine sniffing, resident-intruder, and social interaction tests. They also displayed increased risk taking activity in the elevated plus maze test, and slept/rested less during home cage activity monitoring. Chronic, but not acute, treatment with lithium rescued the hyperactive and risk-taking behaviors, as well as some of the increase in goal-directed behavioral phenotypes. These data illustrate that the GluR6 KO mouse strain is a potential genetic model for mania and excessive behavioral excitement.

Some human genetic data suggest that Disrupted in Schizophrenia 1 (DISC1) (Kato 2007) and RAS guanyl-releasing protein 1 (calcium and DAG-regulated) (RASGRP1) (Ferreira et al. 2008) may both be implicated in risk for BPD. DISC1 (Shinoda et al. 2007) and RASGRP1 are known modulators of the extracellular signaling regulated kinase (ERK) pathway. A postmortem study found that protein levels of the multiple components of the ERK pathway were lower in cortical tissue from victims of mental illnesses including BPD (Yuan et al. 2009). Several studies have shown that chronic treatment with the mood stabilizers, lithium or valproate, activated the ERK pathway, increased the expression of ERK regulated genes including B-cell lymphoma 2 (Bcl-2) and brain-derived neurotrophic factor (BDNF), and promoted the morphological function of ERK pathways, such as neurite growth, neurogenesis, and neuronal survival against a variety of insults (Creson et al. 2009; Einat et al. 2003; Engel et al. 2009; Hao et al. 2004; Hunsberger et al. 2009a; Yuan et al. 2001). ERK1 is one of two ERKs in the pathway. Multiple tests found that ERK1 ablation in mice resulted in hyperactivity (Engel et al. 2009; Mazzucchelli et al. 2002; Selcher et al. 2001), more locomotor activation in the amphetamine challenge test (Engel et al. 2009), increased response to morphine (Mazzucchelli et al. 2002), and cocaine in the place preference test (Ferguson et al. 2006), and enhanced development of cocaine-induced behavioral sensitization (Ferguson et al. 2006). ERK1 null mice also appeared to have increased goal-directed behavior in the active avoidance test (Mazzucchelli et al. 2002), the forced swim test (Engel et al. 2009), and home cage wheeling running (Engel et al. 2009); they also displayed increased risk-taking in the open arms of the elevated plus maze test (Engel et al. 2009) and more rearing in the open field (Engel et al. 2009). This hyperactive phenotype was rescued through treatment with valproate and olanzapine (an atypical antipsychotic with mood-stabilizing effects). Treatment with lithium, valproate, or olanzapine rescued increased response in the amphetamine challenge test (Engel et al. 2009). Together, the data provide reasonably strong evidence to support ERK1 null mice as a genetic model for mania and excessive behavioral excitement.

It is worth emphasizing that excessive behavioral excitement is a unique phenotype resulting from manipulation of certain genes expressed in the brain, though not all of them. For instance, GluR1 KO mice were hyperactive (Wiedholz et al. 2008), but showed reduced duration in the social investigation test (Wiedholz et al. 2008) and more anxious-like behaviors in the elevated plus maze test (Mead et al. 2006). In addition, other mutant strains also display a few or several features of excessive behavioral excitement, but data regarding whether mood stabilizers rescue these phenotypes have not yet been reported. For example, mice overexpressing GSK-3b, a known direct and indirect target of lithium and valproate, were hyperactive in the open field and forced swim tests; however, it remains unknown

whether these mice also display increased risk-taking and drive, and less sleep/rest in the home cage, or whether the phenotype responds to treatment with mood stabilizers (Prickaerts et al. 2006). Interestingly, knocking out the long form of NCAM resulted in a different phenotype from all-forms NCAM null mice (see discussion above). These 180 kDa null mice showed increased aggression in the resident intruder test, less anxious-like behavior in the elevated plus maze test, and less immobility and more swimming in the forced swim test (Stork et al. 2000). Although the overall phenotype is very suggestive, whether or not the phenotype can be classified as excessive behavioral excitement related to mania cannot be further assessed unless data from treatment and additional behavioral studies become available.

4 Partial Models for Affective Vulnerability or Resilience (Table 3)

BPD is a recurrent illness; patients between mood episodes are considered to be in the euthymic phase. Euthymic BPD patients can respond to emotional, social psychological, or physiological (such as jetlag and lack of sleep) stress/insults with a full-blown depressive or manic episode (Belmaker 2004; Goodwin and Jamison 2007). For instance, although psychostimulants can cause mood changes in healthy subjects, the same dose can result in full-blown mania in an euthymic BPD patient (Anand et al. 2000). Furthermore, monoamine depletion can cause mild mood disturbance in healthy controls, but a full-blown major depressive episode in euthymic patients with mood disorders (Ruhe et al. 2007). Thus, elucidating the genetic, molecular, and cellular mechanisms underlying these affective endophenotypes for BPD is essential for developing treatments that can prevent, or even cure, BPD.

Several behavioral paradigms using either acute or severe stress approaches (e.g., the learned helplessness paradigm) (Maeng et al. 2008) or chronic but relatively mild stress approaches [for a review see Willner (1995, 1997), Willner and Mitchell (2002)] are associated with anhedonia-like displays along with other behavioral abnormalities. Preliminary data also suggest that monoamine depletion can induce anhedonia-like displays. The amphetamine challenge test and psychostimulant-induced behavioral sensitization paradigms have been used as experimental models for the pathogenesis of mania [for a review see Einat (2006), O'Donnell and Gould (2007)]. Similarly, a paradigm of sleep deprivation-induced cluster of behavioral alterations has been reported for the pathogenesis of mania (Benedetti et al. 2008). Some of these paradigms or tests have been used to study suspected genes for affective vulnerability or resilience using genetically manipulated mice. However, such studies on affective vulnerability and resilience in animals are, overall, still in their early stages and more data are needed to further assess the promising potential models described below.

Dysfunction of the hypothalamic pituitary axis (HPA) is known to contribute to the etiology of MDD and BPD (Wei et al. 2004). Neuronal glucocorticoid receptor (GR) overexpression (GRov) mice displayed increased anxiety-like behaviors in the elevated plus maze and light dark box tests, and increased immobility in the forced swim test (Wei et al. 2004). These alterations were rescued through treatment with antidepressants (Wei et al. 2004). In addition, GRov mice displayed aggravated cocaine-induced behavioral sensitization (Wei et

al. 2004). Taken together, these data support the GRov mouse strain as a promising potential model for affective vulnerability.

Although it was first discovered as a major antiapoptotic protein expressed throughout the body, Bcl-2 is now also known to play a major role in a variety of brain functions [for a review see Hunsberger et al. (2009a, b)]. Treatments with mood stabilizers and antidepressants upregulate Bcl-2 levels (Chen et al. 1999; Creson et al. 2009); the upregulation by mood stabilizers is believed to occur via ERK/AKT-CREB-gene transcription mechanisms (Creson et al. 2009). Clinical studies have shown that Bcl-2 SNPs are associated with brain gray matter volume (Salvadore et al. 2009) and response to citalopram treatment (Hunsberger et al. 2009a, b). Lower Bcl-2 levels were also observed in the postmortem brain tissues of individuals with BPD (Kim et al. 2009). Furthermore, Bcl-2 heterozygous mice, which have approximately 50% of the Bcl-2 brain levels of wild-type mice, were more anxious-like (Einat et al. 2005) and exhibited enhanced amphetamine behavioral sensitization (Lien et al. 2008), suggesting that Bcl-2 HET KO mice are a promising potential model for affective vulnerability.

Bcl-2-associated athanogene (BAG1) is a Bcl-2-related protein known to function in ER and mitochondria and to modulate calcium homeostasis and intracellular signaling of steroid receptors including GRs. Chronic treatment with lithium and valproate upregulated hippocampal mRNA and protein levels of BAG1 and modulated BAG1-mediated GR nuclear translocation in primary neuronal cultures (Zhou et al. 2005). GR nuclear translocation is also known to be mediated by FK506 binding protein 5 (FKBP5), a gene implicated by some genetic studies in MDD, BPD, posttraumatic stress disorder (PTSD), and the therapeutic actions of antidepressants (Binder et al. 2008, 2004; Kato 2007; Lekman et al. 2008; Tsai et al. 2007; Willour et al. 2009). Mice with neuronal overexpression of BAG1 appeared normal in the open field and forced swim tests and displayed slight and significant increases in open arm activity in the elevated plus maze test, increased recovery from helplessness in the learned helplessness paradigm, increased recovery in the amphetamine-induced hyperlocomotion test, and attenuated response in the cocaine-induced behavioral sensitization test (Maeng et al. 2008). Conversely, BAG1 heterozygous knockout mice exhibited reduced recovery from helplessness and enhanced cocaine-induced behavioral sensitization (Maeng et al. 2008). Together, these data support that BAG1-overexpressing and BAG1 HET KO mice have features resembling affective resilience and vulnerability, respectively.

5 Cyclicity

Cyclicity spontaneously alternating between mania and depression is a unique feature of BPD, although a huge range of swing intervals exist among patients. Simulating this feature in rodents requires long-term activity monitoring with equipment, such as a video recording system or a running wheel. Wheel running activities, for instance, are known to alternate in female rodents along with the estrous cycle. Mitochondrial dysfunctions in BPD have been implicated by human genetic, peripheral tissue, and postmortem brain studies [for a review see Kato et al. (2007)]. Mice with neuronal expression of mutant mitochondrial DNA polymerase (mPOLG) were found to have an accumulation of biological changes resembling

those in humans (Kasahara et al. 2006). Specifically, mPOLG transgenic mice displayed changes in activity patterns within the day night cycle (Kasahara et al. 2006). Female mPOLG transgenic mice showed marked increases in activities synchronized with the estrous cycle, and these changes were rescued by lithium treatment (Kasahara et al. 2006). One interpretation of these data is that mPLOG expression serves as an amplifier and modifier of long-range (several days) periodic activity; however, the genes and molecular machinery responsible for this cycling of mood and activity cycling have yet to be revealed.

6 Closing Remarks

BPD comprises at least four core features depression, mania, mood vulnerability, and cyclicity all of which remain to be fully understood at the molecular, cellular, and neuronal circuitry levels. These clinical features of BPD likely result from genetic polymorphisms, previous (especially early life) and ongoing environmental insults, as well as the interaction between the two. Studies using genetically manipulated animals are pivotal in evaluating the role of the gene being manipulated and its impact on behavioral alterations related to BPD, in elucidating the mechanisms leading to BPD-related behavioral alterations, and in assessing the potential efficacy of novel therapeutics for mania, depression, and mood episode recurrence. For this purpose, several partial genetic models for depression, mania, and affective vulnerability have been described with reasonable constructive validity, reasonable to comprehensive face validity, and strong predictive validity. These models do not simulate BPD as a whole. However, feature-by-feature studies and feature-specific models provide important information about the components of BPD. Obtaining this information is an essential step toward creating a comprehensive understanding of BPD and toward building a multiple-featured animal model of BPD in the near future.

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Table 1

Partial genetic models for depression and anhedonia

Clinical features	p11 ^{-/-}	Vmat2 ^{+/-}	NCAM ^{-/-}
Depressed mood	Cannot be assessed	Cannot be assessed	Cannot be assessed
Anhedonia	Less sucrose consumption in the SPT	Less sucrose preference in the SPT	Lack of sucrose preference in the SPT
Weight or appetite change	No data	No changes in food consumption or body weight	No data
Sleep disturbances	No data	No data	No data
Psychomotor activity change, agitation or retardation	More immobility in the TST and FST	More immobility in the TST and FST; less locomotion in the OFT	More immobility in the TST; more locomotion in a large cage and in the OFT
Lost physical strength	More immobility in the TST and FST	More immobility in the TST and FST; less locomotion in the OFT	Inconclusive
Low self esteem	Cannot be assessed	Cannot be assessed	Cannot be assessed
Cognitive disturbances	No data	No data	No data
Hopelessness	Cannot be assessed	Cannot be assessed	Cannot be assessed

SPT Sucrose or saccharin preference test, *TST* Tail suspension test, *FST* forced swim test, *OFT* open field test

Table 2

Partial genetic models for mania and excessive behavioral excitement

Clinical features	mCLOCK	GluR6 ^{-/-}	ERK1 ^{-/-}
Elevated, expansive, or irritable mood	Cannot be assessed	Cannot be assessed	Cannot be assessed
Inflated self-esteem or grandiosity	Cannot be assessed	Cannot be assessed	Cannot be assessed
Flight of ideas or racing thoughts	Cannot be assessed	Cannot be assessed	Cannot be assessed
Increase in goal-directed activity	More activity in the OFT Less immobility in the FST More preference for sweet solutions in the SPT More reward sensitivity in the ICSS More preference in the CPP More escapes in the LHP	More activity in the OFT Less immobility in the FST More preference for sweet solutions in the SPT More sniffing in the FUST More activity in the SIAT More aggression in the RIT	More activity in the OFT Less immobility in the FST More wheel running activity More preference in the CPP
Excessive involvement in pleasurable activities that have a high potential for painful consequences	More risk-taking in the EPM More risk-taking in the RAT	More risk-taking in the EPM	More risk-taking in the EPM
Decreased need for sleep	More activity and less rest in home cage	More activity and less rest in home cage	More activity and less rest in home cage
Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	No data	No data	No data

OFT open field test, *FST* forced swim test, *SPT* Sucrose or saccharin preference test, *ICSS* intracranial self-stimulation, *LHP* Learned helplessness paradigm, *EPM* Elevated plus maze, *RAT* Reward/Aversion Test, *FUST* female urine sniffing test, *SIAT* social interaction test, *RIT* resident-intruder test, *CPP* conditioned place preference test

Table 3

Partial genetic models for affective vulnerability or resilience

Clinical features observed in susceptible individuals	GRov	Bc1-2 ^{+/-}	BAG1ov	BAG1 ^{+/-}
Circadian shift causes mood changes	No data	No data	No data	No data
Psychostimulants trigger manic episodes	More sensitive to cocaine in the PIBSP	More sensitive to amphetamine in the PIBSP More locomotion in the AIH	Increased recovery in the AIH	More sensitive to cocaine in the PIBSP
Monoamine depletion causes depressive episodes	No data	No data	No data	No data
Stress triggers depression or mania	More immobility in the FST	No changes in the FST More vulnerability to helplessness in the LHP Less spontaneous recovery from helplessness in the LHP	Increased recovery from helplessness in the LHP	Less spontaneous recovery from helplessness in the LHP

GRov glucocorticoid receptor (GR) overexpressing mice, BAG1ov BAG1 overexpressing mice, PIBSP Psychostimulant induced behavioral sensitization paradigm, FST forced swim test, AIH amphetamine-induced hyperlocomotion test, LHP Learned helplessness paradigm