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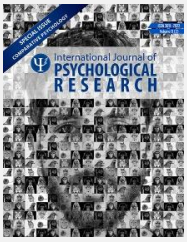
Una visión general de los modelos en ratón: una clave para la comprensión de los subtipos de manía



Review

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ABSTRACT

Animal models have been broadly used in the study of pathophysiology and molecular and neurochemical pathways in neuropsychiatric diseases. Different approaches have used both consanguineous and non-consanguineous mice models to model behavioral patterns associated with the maniac spectrum. However, the disadvantages of validating clinical and experimental protocols have hindered the replication of these studies. In this article, the advantages and disadvantages of using consanguineous lines and non-consanguineous stocks in mice animal models for the study of mania and its subtypes are discussed. Additionally, new experimental alternatives to advance the pathogenesis and pharmacogenetics of mania using animal models are proposed and analyzed

Palabras clave: modelos animales, trastorno afectivo bipolar, knockout y manía.

RESUMEN

Los modelos animales se han utilizado ampliamente en el estudio de la fisiopatología y vías moleculares y neuroquímicos en enfermedades neuropsiquiátricas. Diferentes enfoques han utilizado modelos de ratones consanguíneos y no consanguíneos para modelar patrones de comportamiento asociados con el espectro maníaco. Sin embargo, las desventajas de la validación de los protocolos clínicos y experimentales han obstaculizado la replicación de estos estudios. En este artículo, se discuten las ventajas y desventajas del uso de líneas consanguíneas y no consanguíneas en modelos animales de ratones para el estudio de la manía y sus subtipos. Además, se proponen y analizan las nuevas alternativas experimentales para avanzar en la patogénesis y la farmacogenética de la manía utilizando modelos animales.

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1. INTRODUCTION

The understanding of bipolar disorder has had substantial changes in the last 10 years. Currently, our concept of mania and especially manic states has included a great variety of symptoms which can contribute to the clinical discrimination of the presence of subtypes and thus delineate differential diagnoses within bipolar spectrum disorders. Even though the presence of mania can derive from viral infections, head trauma and other neurological conditions, its expression is also narrowly related to bipolar disorder. Our analysis begins with and aims to deepen the understanding of this disorder.

Bipolar disorder affects 1 to 4% of the general population and has been frequently associated with high rates of mortality and morbidity (Saunders and Geddes 2016). This situation is reflected in the study performed by Fiona J Charlson et al in 2016, which shows high mortality rates in bipolar patients (Charlson, et al. 2016). This can be explained in large part due to the high prevalence of bipolar disorder worldwide, with 58.9 million cases reported by 2010 (Degenhardt, et al. 2013).

Mania is generally characterized by the presence of an abnormally euphoric and exalted mood state. In addition, for manic patients irritability, distractibility and inhibitory control failures significantly affect the performance of daily activities. In many cases, the impact on functionality is unfortunate and can lead to negative effects in both the social and cognitive performance of these patients. Particularly in type I Bipolar Disorder, in which mania predominates, the combination of the disorder with functional deficits related to disruptive conduct leads to neurocognitive changes, specifically a deterioration in executive functions such as processing speed, executive attention, work memory, and decision-making. Although new clinical intervention strategies to control or reduce bizarre behavior do exist, approaches that address cognitive dysfunction in Bipolar Disorder are still limited (Bora, et al. 2016; Cotrena, et al. 2016; McCormack, et al. 2016).

Different personalized medicinal alternatives to treat the symptoms of manic episodes have recently been developed: clinical instruments that refine the manic spectrum; advances in pharmacogenetics based on the use of computational models to discern molecular biology; and advances in our understanding of metabolic pathways and the kinetic properties of medication used for the treatment of mania. The latter has the aim of recognizing the neurophysiological significance of the molecules that play an important part in the manic spectrum.

In this context, the use of animal models in the study of mania was initially crucial to prioritizing pharmacological strategies. The first approaches were conducted on mice with the use of psychostimulants to increase motor activity as one of the observable behaviors present in mania. However, and particularly in the use of stimulants, the phenotype related to increased motor activity is shared with other clinical phenotypes like anxiety and drug abuse, conditions which were not found to be sufficiently consistent to validate an animal model with this phenotype for mania. In this article, we analyze the phenotypes that were found to be potentially informative in rodents, and that could contribute to the modeling of neurobiological pathways in mania. This analysis is directed towards finding new therapeutic targets and allowing the discrimination of different subtypes of bipolar disorder.

2. ANIMAL MODELS

The use of rodents has sped up the development of potential therapeutic objectives in different diseases. Furthermore, in the study of behavior it has established an experimental preference matrix to model illnesses related to psychiatric disorders. In laboratories, two types of genetically defined mice models have been used. Consanguineous lines, as a prototype of genetically standardized lines, allow control over the genetic constitution of individuals (Chow 2016), eliminating the inconveniences of populational stratification and encouraging genetic homogeneity in the model. Additionally, laboratories have monitored endogamy levels and supervised endogamic depression (which can lead to the loss of the line or impact the adaptation

of the animals to their environment, affecting the behaviors of interest).

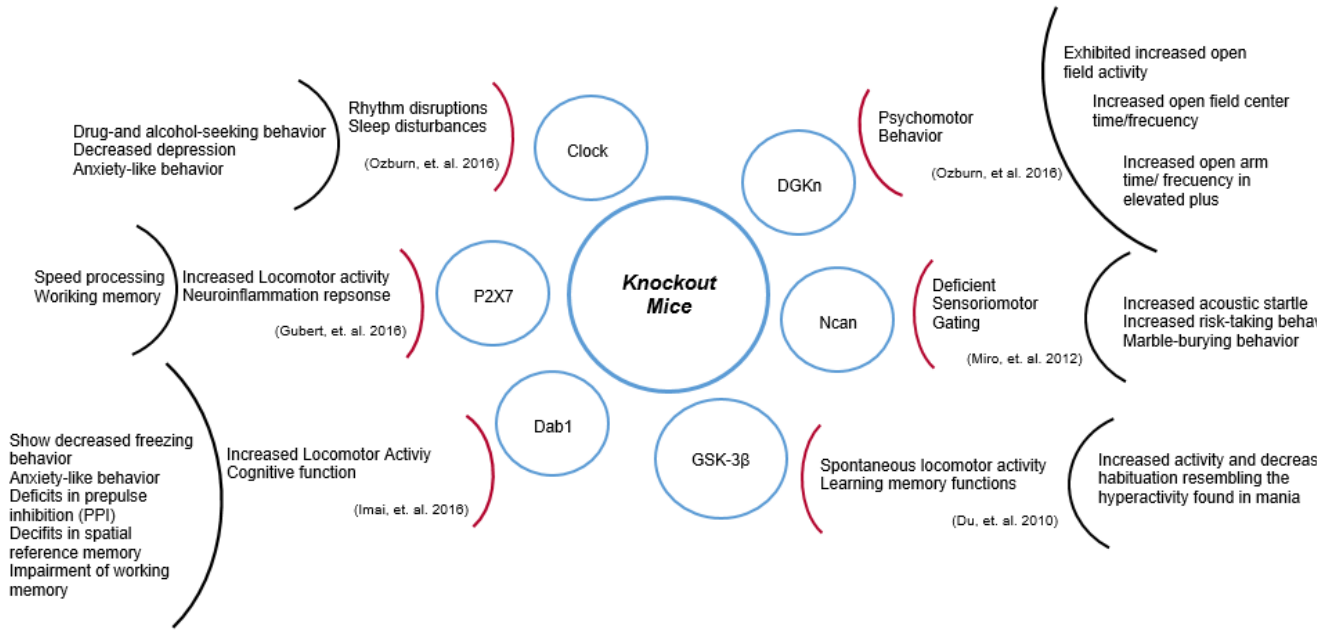
Consanguineous lines have guided researchers toward different potential targets with pharmacogenetic therapeutic purposes because allele fixations set an ideal genetic scenario for the evaluation of the association between drugs and allelic variants due to the isogenicity of the lines. Therefore, different studies that aim to improve the efficacy of pharmacology in treating bipolar disorder have used consanguineous lines. Knockout mice (KO) have been a promising alternative. These mice are modified by genetic engineering and allow the identification of the role of a particular gene based on the identification of its amino acid sequence in its etiopathogenesis or in the action mechanisms of various drugs with unknown functions. For example, to determine the pathophysiological impact of Glycogen synthase kinase 3beta (GSK 3beta) on KO mice, the potential of new GSK-3 inhibitors were evaluated using the consanguineous line C57BL, one of the most used by comparative genomics and the line chosen by the International Mouse Sequencing Consortium for the sequencing of the murine genome. GSK-3beta is a serine/threonine protein kinase with high concentration in the brain, where it modulates gene expression and neural plasticity among other neurodevelopment processes (Frame and Cohen 2001; Furlotti, et al. 2015). Recent studies suggest that the inhibition of GSK3beta through the increase of serine phosphorylation modulates the pharmacological response and reduces observable hyperactive behavior in this model. This is similar to the response to lithium which also increases serine phosphorylation and reduces the antimanic response (Li et al. 2010). On the other hand, KO mice have also been used in attempts to modulate hyperactivity and homogenize the accelerated motors of the mice and control the uninhibited and disorganized behavior of the manic phase. From this perspective, DGKη-knockout was used to determine how the function of diacylglycerol kinase (DGK) is related to the neurogenic mechanisms involved in mania and illuminated its important role in cognitive function, particularly in memory and emotional regulation. Nevertheless, the molecular pathways that underlie the clinical expressions related to mania and could be associated with the differential expression of DGK have not yet been determined (Isozaki, et al. 2016).

The mice line Dab1 has been used similarly to explore the neurophysiopathology of the manic spectrum. Dab1 is an intracellular adaptive protein involved in signal processes and neuronal function linked to Reelin, a cellular migration glycoprotein that promotes the maturation of dendritic spines and also contributes to synaptic modulation and memory function (Jacquelin, et al. 2013). The Reelin-Dab1 complex is key to both motor function and the expression of social conduct. Currently, alterations in motor function, spatial memory, and contextual fear memory have been observed in Knockout Dab1 mice. Additionally, a decrease in the expression of Reelin-Dab1 complex in the cerebral cortex produces strange behavior as well as learning and memory deficits (Imai, et al. 2016). Perhaps one of the most robust approaches to modelling a behavioral pattern related to the manic spectrum came from studies that implemented the chronic administration of stimulants such as amphetamine (AMPH), which was able to produce an effect on the inhibition of dopamine reuptake (Fries, et al. 2015; Macedo, et al. 2012). To determine how long term treatment with AMPH could be involved in the pathogenesis of mania, Gubert et al. used KO for the purinergic receptor P2X7R. Purinoreceptors are present in cells of the immune system and are widely distributed in nerve terminals, affecting the release of neurotransmissors like glutamate or GABA, and constitute a modulating agent in the concentration of intracellular calcium. With this line researchers were able to determine that there was a significant increase in motor activity and establish a proinflammatory response associated with the presence of cognitive deterioration in functions like work memory and processing speed in patients with bipolar disorder (Cuartas 2014; Gubert, et al. 2016; Suadicani, et al. 2006).

Beyond phenotypes frequently associated with mania like changes in motor function and hyperactivity, another alternative has been to

explore circadian rhythms using KO models. There is no doubt that irregularities in hormones, sleep cycles, and chronotypical variations are closely related to the expression of mania. Therefore, the proteins involved in the molecular clock have become a therapeutic target in murine models. The Clock knockout has allowed the identification of the functional consequences of some polymorphisms in the genes that regulate the molecular pathways of circadian rhythms. In the case of Per1 (one of the CLOCK genes), the variant 3111T/C alters transcriptional efficiency and therefore the physiological processes that control sleep-wake dynamics, body temperature, and the hormonal changes related to the molecular clock (Ozburn, et al. 2016).

Figure 1. *Most-used KO animal models in mania (blue), domains (red) and phenotypic related subdomains (black)*



Although some animal models, particularly KO, are not considered explicit animal models by many researchers, they have helped select molecular targets that underlie the complex expression of mania in humans. However, the weakness of this model lies in the difficulty of standardizing the expression of a behavior. For example, increased motor activity or hyperactivity as an exclusive condition for mania that with difficulty emulates the presence of an episode of extreme irritability, uninhibited behavior, or even behavioral disorganization. Therefore, the use of consanguineous mice or any genetically modified animal cannot itself constitute a standard comparative animal model of the expression of behaviors of interest in mania. Underlying these behaviors is the participation of various widely-distributed molecular targets that produce an incalculable number of results that have not been consistently replicated in the etiopathogenesis of the manic spectrum.

Additionally, due to the methodological limitations and costs associated with the use of KO models, researchers have used stocks of non-consanguineous animals, which are much cheaper than consanguineous lines and allow for the control of the endogamy rate, which shouldn't exceed 1% per generation (Festing 1993). One of the most popular mice colonies for this research has been the Black Swiss, which has been used to model behavior repertories like reward-seeking, risk-taking behavior, aggression, hypersexuality, hedonia-like behavior, inattention, and the response to psychostimulant drugs.

These stocks have also been used to explore cognitive repertories which manifest

deficits in inhibitory control, observable through measurements of the startle response (SR) and prepulse inhibition (PPI) paradigms (Sanchez-Morla, et al. 2016). These have been evaluated with non-consanguineous mice as an alternative way to trace nuclear psychophysiological matrices within the cognitive phenotype and to explain the evolution of clinical variables in mania. One example that is relatively parsimonious is the activation of the sensory-motor response mediated by emotional valences as a strategy to refine behavior observation (Levin, et al. 2011; Ong, et al. 2005; van Enkhuizen, et al. 2015).

SR is the fastest activated reaction of human and animal motor systems, and PPI is one of the mechanisms that regulates it. The SR that comes from an involuntary activation of the motor tract, with origins in the encephalic trunk and whose response and latency magnitude has shown intraindividual variation, where women manifest a greater SR than men, probably depending on sensorial entry (Kofler, et al. 2001).

In this context for different mania subtypes, the most important aspect to consider about the modulation of RS may be PPI because it controls or restricts access to information about irrelevant stimuli and it gives a cognitive hierarchy to the information that enters, facilitating the sequence and planning of behavior (Blumenthal, et al. 1996). For now, one of the experimental approaches to SR-PPI, through which we get most of our information about the neurobiology of sensory-motor responses, comes from the acoustic startle response (ASR) (Koch 1999).

In this context, PPI deficits, particularly of the acoustic type, have been associated with the manic spectrum (Douma, et al. 2014). Undoubtedly the stock of non-consanguineous animals helps to determine their success as psychophysiological markers of trait/state, and mark the neuropathophysiological pathways that are potentially involved in the expression of mania. Along with SR changes and PPI modulation, other behavioral repertories like reward- and sensation-seeking can be expressed differently in mania, suggesting responses that are neurophysiologically different according to the manic subtype (see figure 2).

Responses to the three most prevalent behavioral patterns in mania have been modeled in mice: irritability, a domain related to resident intruder which is observable in approximately 70% of patients; hyperactivity, which is present in 90% of manic states and is modeled in animals through the increase in motor activity; and sleep deprivation, common in 80% of patients in the manic phase (Goodwin FK and 2007; Young, et al. 2011). With all of these findings, the use of non-consanguineous mice has failed to establish a robust model approximating the manic spectrum, and there are still limitations in modeling the putative neuropathophysiological signals that operate in mania.

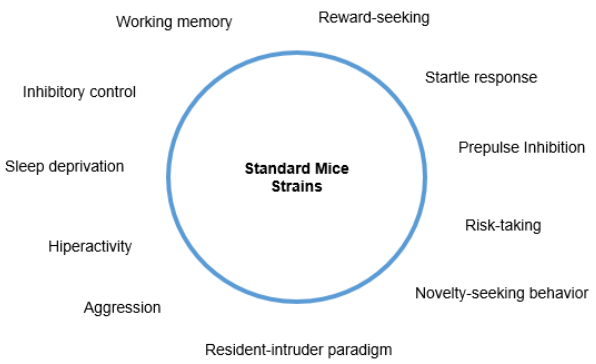
The use of mice to model behavior is not specific to mania, and most evaluated behavioral repertories are inherent to several mental disorders. This suggests distinct etiopathogenic pathways. For example, one of the most sensitive models to simulate mania in mice has been the sensitization model mediated by psychostimulants, which produces psychomotor agitation and hyperactivity. However, this is not exclusive to mania, because the intermittence of manic episodes suggests additional mechanisms involving other neurochemical pathways along with the increase and reuptake of dopamine generated by the psychostimulant.

Given the lack of consistency of some of the behavior signs in the use of these models and in the subtypes of mania, different studies have tried to outline an experimental path that discriminates between different cortical areas and cognitive dysfunction, principally that which is most frequently observable in the manic spectrum as performance in executive function, attention, verbal fluency, and work memory. Approaching a neurofunctional representation of the cortical regions associated with these cognitive functions, especially the dorsolateral prefrontal, anterior cingulate, parietal, and temporal, has allowed the construction of a neurophysiological and molecular network to explain the differential expressions of the cognitive disturbances observable in mania.

On this question, Ersland et al. found similar functional annotations for homologous

genes in humans and rats in frontal and temporal areas which could give functional clues to cellular communication mechanisms, intracellular signaling cascades, signal transduction, emryogenesis, and neurogenesis, potentially associated with cognitive dysfunction in mania (Ersland, et al. 2012; Le-Niculescu, et al. 2009). For example, changes in the expression of the brain-derived neurotrophic factor (Bdnf) in mice are associated with deterioration in work memory and present dorsolateral correlation. In the same way, Dbp (D-box binding protein) and Per1 (period circadian protein homolog 1) genes involved in the circadian rhythm and prefrontal correlation suggest a singular etiopathogenic pathway in the expression of subtypes in mania (Stansberg, et al. 2011).

Figure 2. *Most-used physiological and behavioral patterns to model different subtypes in mania with the use of non-consanguineous mice.*



While comparisons between humans and mice could generate methodological bias because of the difference in size, connectivity, and cortical areas, some patterns of cortical organization are relatively universal among major mammal groups. Zones of great cortical similarity can be observed particularly in the primary auditory area and the primary and secondary visual areas, in part because of the expression of common inheritable genetic patterns among all mammals. From this reference point, recent findings have been able to identify some common genetic patterns between rodents and humans that allow the recognition of differential functional specialization in both species (Chen, et al. 2011).

Additionally, for mania subtypes, altered or differential protein expression in some zones of the brain involved in the phenotype of interest could favor the development of strains or lines of animals in which molecular changes that have previously been observed in those individuals that exhibit the manic phenotype can be identified. It's worth noting the need to review and verify the validity of the content in constructive and predictive terms for these translational approaches.

For now, and in the interest of deepening the mechanisms involved in the etiopathogenesis of mania with the use of animal models, several alternatives have been proposed:

3. THE INTERNATIONAL CONSORTIUM ON LITHIUM GENTICS (CONLIGEN)

Without a doubt lithium sets a putative neurobiological pathway for bipolar disorder. Lithium has a broad intercellular action mechanism. It regulates the sodium pump (Na+/K+-adenosintrifosfatasa), acts on G proteins, modulates the phosphatidylinositol cycle, and inhibits the adenylyl cyclase AMPc system. Because of this, ConLiGen came out of the attempts to identify effective neuropharmacological targets related to the response to lithium in the intervention in bipolar disorder. ConLiGen's main objective is defining the phenotype that responds to lithium, analyzing its pharmacogenetic aspects and also limiting its adverse effects, while keeping in mind the differential genetic susceptibility (due to the populational ethnic component).

Currently three genome-wide association studies (GWAS) have been performed. Their findings have not been consistently replicated, probably due to the genetic heterogeneity of the populations from which patients were recruited, small sample sizes, and possibly the use of different clinical protocols to define the phenotype. ConLiGen recently published a GWAS on lithium

response in approximately 2500 patients, using rigorous scales for clinical evaluation, controlling interevaluator reliability and applying ancestry controls in the sample, allowing them to identify long non-coding RNA sequences (lncRNA) (Hou, et al. 2016).

LncRNAs could act as regulators of genetic expression though a series of mechanisms like chromatin modifications, the increase of the transcription and degradation of mRNA. These findings need to be replicated to begin functional genomic studies. However, they contribute to deciphering the fundamental molecular pathways in those patients with good therapeutic responses to lithium as one of the clinical subtypes of bipolar disorder. The recognition of highly-conserved cellular processes that we share with mice brings about the need to evaluate the mechanisms involved in the response to lithium in animal models. The findings obtained by ConLiGen generate alternative ways to model new therapeutic targets and the experimental use of mice would refine these findings.

4. MODELLING NEUROPROGRESSION IN MANIA

Evaluating the evolution of mania through time is a challenge for phenomics. The phenomenology of mania establishes particular subtypes of progression, namely: higher episode frequency; decrease in the interval between episodes; negative evolution in the response to treatment; and progressive and variable evolution in neurocognitive deterioration. These combine with structural changes in some regions of the brain. An experimental model to determine the neuroprogression of recurrent mania in mice could trace putative pathophysiological pathways in mania (Sharma, et al. 2016). An example of this would be the controlled exposure for temporary intervals to a psychostimulant or domaminergic inhibitor, promoting the expression of behavior responses that correlate with the neuroprogression of mania in humans.

5. THE USE OF DESIGNER RECEPTORS EXCLUSIVELY ACTIVATED BY DESIGNER DRUGS (DREADDS)

The lack of robust technology, reversibility, and special-temporal control has limited the consistency of behavior studies in comparative biology. Consequently, the recognition of how molecular and neurochemical networks mediate the expression of behavioral patterns in both a short (minutes to hours) and long (days to weeks) time reference constitutes a challenge in modelling behaviors associated with mental illnesses in periods of evolution, change and maintenance of conduct, due to spatiotemporal limitations.

The use of DREADDs allows the pharmacological activation or inhibition of specific neuronal groups through signaling pathways coupled with G proteins. (Urban, et al. 2016). This neuropharmacological mechanism, which uses modified protein receptors, has applications for psychiatry and animal models.

In mania, one of the phenotypes frequently associated with mice has been the increase of motor activity. In this case, DREADDs help to explain behavioral repertories in congruence with the activation of molecular receptors and the characterization of brain circuits in a given brain topology. Currently, DREADDs are an excellent strategy for behavior studies in animal models to evaluate the prolonged effect of neuronal activation or inhibition (Aston-Jones and Deisseroth 2013; Farrell and Roth 2013), potentially associated with the manifestation of behavior related to the manic spectrum. They also facilitate the determination of the functional consequences of the activation of neuronal pathways limited to mania.

6. IMPLEMENT CONVERGENT FUNCTIONAL GENOMICS

With the development of the functional genomics and the recognition of gene sequences and function, along with the recent findings in comparative genomics (Yue, et al. 2014), it has been determined that mice and humans share approximately 70% of the protein-producing

sequences in 1.5% of their respective genomes. Yue et al. found significant correlations for both species in histone modification that suggest critical regions related to neurological diseases, particularly bipolar disorder.

It is precisely these results of conserved gene expression conserved between animals and humans that support the development of translational methodologies like Convergent Functional Genomics (CFG), which integrates Bayesian approaches to evaluate shared patterns in animal models that converge with human beings. While research on bipolar disorder in humans has evolved to refine diagnostic processes that contribute to clinical specificity in mania, the parallel use of animal models has contributed to improving molecular sensitivity. Therefore, CFG incorporates gene expression profiles in animals, which along with human genetic linkage studies promote efficient alternatives in clonal positioning, outlining molecular targets that are relevant to disease pathophysiology (Le-Niculescu, et al. 2008; Niculescu 2013).

7. OPTOGENETICS

Following the discoveries of neurobiological pathways that were articulated by comparative genomics and traslational function, the development of tools that allow the real-time manipulation of neuronal activity in relevant neurophysiological zones has become a crucial experimental methodology for the recognition of the modulation of neural circuits and their temporal variation, promoting the identification of molecular signals of cellular regulation (Sidor and McClung 2014). Optogenetics also allows the analysis of reaction times in the modulation of neural circuits in the expression of a behavior, through the analysis of distribution entropy, similar to analyses performed in thermodynamics. This analysis contributes to explaining how the expression of a behavioral pattern is the reflection of the duration of cognitive processes involved in it (Hong and Newell 2008; Mesik, et al. 2015; Rossi, et al. 2012). It also allows the identification of dysfunctional behavioral patterns in the manic spectrum in terms of intensity, duration or chronicity, and shows the cortical neuroarchitecture and molecular pathways most likely associated with the behavior of interest.

Finally, although animal models have led to progress in the clinical modeling of mania, the results of molecular pathways that provide relevant pharmacogenetic insights and facilitate the discrimination of differential clinical patterns have still not been determined. Mania includes several clinical subtypes that also interact with changes related to early or late onset, a greater or lesser number of crises in a given time frame, and the severity and temporary progression of intercrisis. Furthermore, each subtype can be associated with different physiopathological correlations, which simultaneously are related to molecular bases and distinct genetics, which could configure an intermediate phenotype or endophenotype. The challenge in using non-consanguineous stocks of animals is to always supervise the protocols of content validation, construction, and prediction in the evaluation of the behavior to model. On the other hand, although the use of consanguineous lines as animal models is controversial, they have been advantageous because they reduce the genetic heterogeneity in comparative analyses, simplifying the identification of profiles with expressions in common. This is now possible due to recent results that determined the conserved and shared regions between mice and humans.

Perspectives like optogenetics are the future for the study of the brain. Understanding the changes in neuronal activity that occur in days and weeks in the development of a psychiatric disorder contributes to the determination of which circuits underlie the phenotypical expression relevant to the manic spectrum. Some preliminary studies are directed at studying circadian rhythms and how cortical reward is influenced by alterations in daily activities that refer the activity to a specific neural circuit related to the activity of dopamine in the mesolimbic pathway (Sidor and McClung 2014), demonstrating behaviors in mice that are belong to the expression of mania in humans. However, to overcome experimental difficulties, Optogenetics as a discipline still requires

advances in the thermodynamic stability of proteins and to be able to refine the association of neuronal networks and the expression of behavioral patterns in psychiatric illnesses.

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