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The Contribution of Tonic Inhibition to Cognitive Deficits in a Mouse Model of Bipolar Disease

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Abstract

Introduction: Bipolar Type I is a neurological disorder characterized by manic episodes, hyperactivity, and cognitive deficits. A prevalent feature of this disorder is comorbid sleep disorders. In fact, sleep deprivation has been used to induce a bipolar phenotype in rodent models, through mechanisms not well understood. One possible mechanism is increased tonic inhibition in the hippocampus, a region critical for memory. Tonic inhibition in this region is mediated primarily by γ-aminobutyric acid type A receptors containing the α5 subunit, which regulate neuronal excitability, synaptic plasticity, and memory. Interestingly, tonic inhibition mediated by these receptors is increased in response to sleep disturbances. Therefore, this study aims to 1) determine whether tonic inhibition is increased in bipolar model mice, 2) determine whether increased tonic inhibition contributes to cognitive deficits in bipolar model mice, and 3) determine whether increased tonic inhibition contributes to hyperlocomotion in these mice.

Methods: To model bipolar disorder, mice are sleep deprived using the disk-over-water method. Tonic inhibition in the hippocampus will be bidirectionally manipulated: genetic overexpression will be used to increase inhibition, and optogenetic modifications will be used to reduce inhibition. The altering of tonic inhibition will also be conducted within the sleep deprived mice. These groups will be compared, along with control C57BL/6 mice regarding 1) level of tonic inhibition, using whole-cell voltage clamp recordings, 2) cognition, using the Morris water Y-maze, and 3) manic activity, using a locomotion assay.

Results: Sleep-deprived mice will exhibit increased tonic inhibition, impaired cognition, and hyperlocomotion. Decreasing tonic inhibition in sleep-deprived mice will rescue cognitive function. Conversely, increasing tonic inhibition in non-sleep-deprived mice will induce cognitive deficits similar to sleep-deprived mice. Altering tonic inhibition in the hippocampus will not affect locomotion.

Discussion: By comparing performance between groups using *t*-tests and ANOVAs, this study shows a potential mechanism underlying cognitive deficits in the sleep-deprivation model of bipolar disorder.

Conclusion: Tonic inhibition is a new pathway to consider for treatments and understanding the mechanisms behind Bipolar Type I.

Keywords: bipolar disorder; sleep deprivation; tonic inhibition; hippocampus; α5 $GABA_A$ receptors

Introduction

Bipolar Type I is a neurological disorder characterized by manic episodes lasting at least seven days, a decreased need for sleep, and cognitive deficits [1,2]. This disorder affects about 4.4% of adults across the world population [3]. A prevalent feature of this disorder is the absence of sleep and/or comorbid sleep disorders [4,5]. In fact, preclinical studies have used sleep deprivation to model mania, which suggests that reduced sleep may play a causal role in the development of symptoms [4,6]. However, the mechanisms underlying such sleep deprivation-induced behavioral disruptions remain not fully understood.

One possible mechanism is increased tonic inhibition in the hippocampus. In the central nervous system, the main inhibitory neurotransmitter is γ-aminobutyric acid (GABA) that acts primarily on ionotropic GABA type A ($GABA_A$) receptors [7]. Depending on the receptor location and composition, inhibition can be considered "phasic" or "tonic" [8]. Phasic inhibition is mediated by $GABA_A$ receptors at the synapse, whereas tonic inhibition occurs primarily through extrasynaptic receptors in response to ambient GABA [8]. In particular, extrasynaptic receptors containing the α5 subunit (α5$GABA_A$ receptors) are critical for mediating tonic inhibition in the CA1 region of the hippocampus [9]. These receptors regulate neuronal excitability and synaptic plasticity, thereby contributing to cognitive function [10]. Increased α5$GABA_A$ receptor-mediated tonic inhibition in the hippocampus has been shown to disrupt synaptic

plasticity, as well as impair memory and executive function in various disease models [11,12].

It remains unknown whether increased tonic inhibition in the hippocampus contributes to behavioral deficits in the sleep-deprivation mania model. However, a recent study showed that sleep deprivation increases tonic inhibition in the hippocampus, due to increased α5GABA$_A$ receptor function [13]. Given the importance of α5GABA$_A$ receptor-mediated tonic inhibition in cognition, there may be a causation between excess tonic inhibition and behavioral impairments in bipolar disorder. In this article, the proposed research protocol addresses the hypothesis that increased hippocampal tonic inhibition contributes to deficits observed in the sleep deprivation model of mania.

Methods

Experimental Mice

Two male mouse lines will be used for the studies. The C57BL/6 strain will be used for *in vivo* and *ex vivo* assessment of the sleep deprivation model of mania, and for studying the effect of overexpression α5GABA$_A$ receptors. The α5-GABAR-E125C knock-in mouse line (α5-E125C-KI), developed by Davenport et al (2019) will be used in *in vivo* and *ex vivo* experiments studying the effect of reducing tonic inhibition [14].

Sleep Deprivation Model of Mania

To induce sleep deprivation, mice will be placed on the "disk-over-water" (DOW) apparatus (Fig. 1A) designed by Rechtschaffen and colleagues [15,16,17] and the procedure by Colavito and colleagues as stated below [18]. The apparatus consists of a cage divided in the middle. There is a rotating disk suspended over shallow water. A control mouse is housed on the opposite side of the "bipolar" mice. The disk rotates once the experimental (bipolar) mouse seems to be entering sleep to force it to stay awake and avoid falling into the water. The control mouse is allowed to sleep when the experimental mouse is awake and functioning as usual without the disk moving. Both mice have unlimited access to food and water and the control mouse is allowed to mostly retain its normal sleep durations.

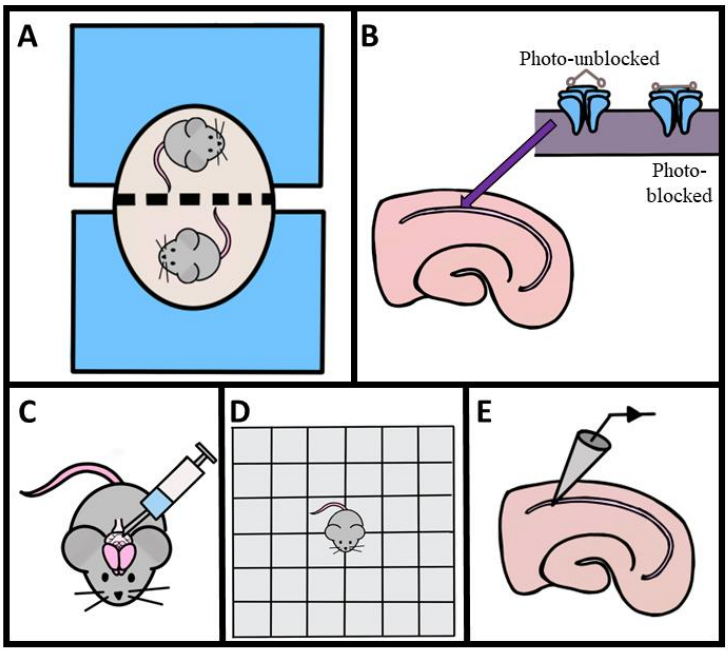

Figure 1. A) Displays the disk-over-water apparatus to sleep deprive experimental mice while allowing control mice to rest. **B)** Optogenetically modified mice have depressed CA1 inhibitory activity through blockage and unblockage of PAG1C to α5 GABA$_A$ receptors. **C)** Increased tonic inhibition via *in vivo* hippocampal injection of lentiviral vectors for the α5 subunit. **D)** Locomotion assay divided into 6 x 6 equal sections. **E)** Electrophysiological recordings done in CA1 hippocampal neurons with a microelectrode. Figure created with procreate.com.

Optogenetically Blocked α5 Subunits

In order to decrease tonic inhibition *in vivo*, GABA$_A$ receptors will be targeted utilizing the techniques developed by Davenport et al [14] (Fig. 1B). Briefly, Davenport and colleagues created a α5-E125C-KI mouse line containing a cysteine mutation in the α5 subunit. α5GABA$_A$ receptors in these mice function normally at rest but can be optically controlled upon the binding of the exogenous ligand PAG1C to the mutant cysteine. Specifically, in the *trans* conformation (in darkness, or in 540-nm light), PAG1C

covers the GABA binding site of the α5GABA$_A$ receptor to prevent activation. In 380-nm light, PAG1C enters a *cis* conformation, uncovering the binding site and allowing normal function.

To reduce α5GABA$_A$ receptor-mediated tonic inhibition *in vivo*, PAG1C will be injected directly into the dorsal hippocampus of α5-E125C-KI mice [14]. A double guide cannula targeted to the dorsal hippocampus will be implanted under general anesthesia, followed by a minimum of 7 days for recovery. Then, to block α5E125C receptors, 1 µL of artificial cerebrospinal fluid (aCSF) containing 250 µM PAG1C and 500 µM TCEP will be injected through the implanted cannula using a Hamilton syringe. Injections will be performed 1 hour prior to the start of behavioral assessment.

Overexpression of α5 Subunits

In order to determine the consequences of increased tonic inhibition *in vivo*, α5GABA$_A$ receptors will be genetically overexpressed using methods developed by Donegan and co-workers [19] (Fig. 1C). Lentiviral vectors for the α5 subunit (pLV-CaMKII-rGabra5-IRES-EGFP; 2.86*109 TU/ml) will be bilaterally injected into the dorsal hippocampus, allowing for targeted overexpression in pyramidal neurons. Mice will recover from the surgery for at least six weeks, to allow for overexpression to reach its peak.

Manipulating Tonic Inhibition in "Bipolar" Mice

To view the connection between tonic inhibition and bipolar models, two other groups of mice utilized are optogenetically modified mice and overexpression mice described above. However, these mice will also be placed on the DOW apparatus after recovery from their imposed treatments with controls to be sleep deprived.

Locomotion in the Open Field

Hyperlocomotion, a hallmark of the mania phenotype in mouse models, will be examined using a locomotion assay [20]. The mice will be placed in a 40 × 60 × 50 cm (l × w × h) open field chamber divided into 36 even square sections (Fig. 1D). The movement of the mice in the open field will be recorded for 60 minutes. Subsequently, recordings will be analyzed using Noldus EthoVision software to quantify the total distance travelled by mice, as well as the number of squares the mice go through.

Cognitive Deficits in the Morris Water Y-Maze

For cognitive deficits the Morris water Y-maze test will be conducted. The Morris water Y-maze is a commercially available maze shaped in a Y, where mice are trained to go to one end of the Y over the other. The Y-maze insert has three long arms 120-degree angles apart. Each arm is 10 cm in width and 30 cm in length. The maze is filled with water so the mice cannot stand and have their head above the water. The end the mouse is trained to go to has a ledge as an indictment since it can stop swimming and instead stand in the maze. After training for a standard time period of 5 minutes in one-minute increments, the mice are set to run 6 trials each approximately 1 minute long. In between each trial, they are kept in a holding cell for 2 minutes. The "correctness" will be measured as the number of times the correct arm was entered out of the total trials. The percentage of time in each arm will also be recorded.

The Morris water maze correct navigations will be tallied to create a proportion of correctness over the trials averaged per treatment group. The data will be analyzed with repeated one-way ANOVAs and t-tests to compare differences in arm entry correctness and time scores in groups as outlined by Dean et al [21]. As with the locomotion analyses, the baseline is determined by the control mice and cognitive deficits must be significantly lower correctness on average per group.

Whole Cell Patch Clamp

Whole-cell voltage clamps will be used to record tonic inhibition in pyramidal neurons of the CA1 in *ex vivo* brain slices (Fig. 1E), similar to previously developed protocols [22]. Coronal brain slices containing the hippocampus will be prepared from adult mice and allowed to recover at room temperature for at least one hour. Subsequently, slices will be moved to a recording chamber, where they will be perfused with aCSF at room temperature. Pyramidal neurons will be visually identified based on morphology and through immunofluorescence in the genetically modified mouse lines.

A high-chloride intracellular solution will be used in the recording pipette to record inhibitory currents, as described previously [22]. Cells will be clamped at a holding potential of -70 mV – once a stable baseline is reached, bicuculline (100 µM) will be applied. The difference in holding current before and after the application of bicuculline will be quantified as the amplitude of the tonic inhibition in the cell. For optogenetic photoswitch treatment, the neuronal slices will be incubated with PAG1C for 45-60 minutes at room temperature. 540 nm (15 mW/cm^2) light will be generated by a Spectra-X LED light source (Lumencor) and delivered via a microscope optical port through a 20X objective.

Mice Across Experiments

For behavioral tests there should be n = 20 mice per group, where n indicates the number of mice. For electrophysiological readings, a sample size of n = 10 will be used per group, where n indicates the number of cells.

Statistical Analyses

All statistical tests will be done in R and the threshold for significance will be p = 0.05. The compiled data will be analyzed per group through ANOVAs to determine the significant differences between treatment groups.

Results

Characterizing the Sleep Deprivation Model

My first step will be to characterize and validate the sleep deprivation model of mania used in the study. Increased locomotion is a hallmark of mania models [23,24] so the outcome in manic phenotypes is hyperlocomotion. Specifically, sleep deprived mice have increased total distance traveled and number of squares entered compared to controls. With regard to cognition, I anticipate that sleep deprived mice will display deficits in the Morris water Y-maze compared to control animals, as demonstrated by taking longer to find the platform and/or spending more time in the incorrect arm of the maze during the trials. Thus, I will confirm that the proposed model demonstrates the expected manic phenotype reported by others [25].

Confirming Properties of α5-E125C-KI

Slices from α5-E125C-KI mice will be perfused with aCSF containing PAG1C, initially in the *cis* conformation. After cells are patched, 540-nm light is shined, switching PAG1C to the *trans* conformation. I expect that the switch will cause a reduction in the holding current, indicating that PAG1C is blocking α5GABA$_A$ receptors, and thereby reducing tonic inhibition.

Confirming α5GABA$_A$ Receptor Overexpression

I will confirm that overexpression of the α5 subunit indeed increases tonic inhibition. I expect to find that in cells overexpressing α5, identified by their expression of the fluorescent marker eGFP, the tonic current amplitude will be greater compared to cells that were not genetically transfected.

Increased Tonic Inhibition in the Sleep Deprivation Model

I hypothesized that sleep deprivation will increase tonic inhibition in the CA1 region of the hippocampus. In support of this hypothesis, I anticipate that the amplitude of the inhibitory tonic current, assessed using whole-cell voltage clamp recordings, will be greater in slices from sleep-deprived mice compared to control mice.

Increased Tonic Inhibition Contributes to Cognitive Deficits in the Mania Model

Having found that tonic inhibition is increased in the sleep deprivation model, I will determine whether this increase in tonic inhibition contributes to cognitive deficits, as reported for other disorders [26]. As described above, I expect that sleep-deprived animals, from either the C57BL/6 or the α5-E125C-KI line, will display cognitive deficits in the Morris water Y-maze. I anticipate that in sleep-deprived α5-E125C-KI mice, reducing tonic inhibition through injection of PAG1C into the hippocampus will markedly improve performance in the maze. Specifically, navigating towards the correct arm and spending less time, if any at all, in the incorrect arm. Furthermore, my hypothesis indicates that increasing tonic inhibition through genetic methods should lead to a similar cognitive phenotype as sleep deprivation. I therefore expect that in the absence of sleep deprivation, C57BL/6 mice genetically overexpressing α5GABA$_A$ receptors in the hippocampus will display cognitive deficits in the Morris water maze similar to sleep-deprived mice. These findings support the hypothesis that increased α5GABA$_A$ receptor-mediated tonic inhibition modulated cognitive deficits in the sleep deprivation model of mania.

Increased Tonic Inhibition Does Not Underlie Hyperlocomotion in the Mania Model

I do not anticipate locomotion to change as a result of altering tonic inhibition in sleep deprived mice for two reasons. Firstly, previous studies have not found convincing evidence that α5 subunit receptors affect locomotion [27,28]. Secondly, the manipulation in this proposal targets the hippocampus, which is a region for memory and spatial recognition, not locomotion [29,30]. Therefore, the total distance traveled, and number of squares entered in the test will be significantly higher in sleep deprived mice than controls and the decrease of tonic inhibition in these experimental mice will not recover control-like behavior.

Discussion

This protocol is designed to address the hypothesis that increased tonic inhibition in the hippocampus contributes to cognitive deficits in the sleep deprivation model of mania. Viewing the changes in tonic inhibition in the "bipolar" model can direct us to observe if tonic inhibition is actually linked to the disorder phenotype. As described above, I anticipate that the findings of my behavioral and electrophysiological studies will support this hypothesis. For each experiment, statistical analyses will be performed in R, using t-tests when comparing two groups, and ANOVAs followed by a Newman-Keuls post-hoc test when comparing more groups. For the Morris water Y-maze, latency to finding the platform as well as time spent in the incorrect arm will be compared between groups. For locomotion, total distance travelled in the open field and number of square crossings will be compared. For electrophysiological studies, the amplitude of the tonic current will be compared.

The recovery of cognitive function shown via improvement of the Morris water maze after decreasing tonic inhibition points to tonic inhibition having a causative role in bipolar disorder. Thus, this pathway will be another route towards recovering normal phenotypes in those affected by the disorder. There is some evidence for this already in the literature since there are current treatments with multiple modes of action not well understood that also affect tonic inhibition [31,32]. In some other disorders and diseases, such as Alzheimer's, attention deficit hyperactivity disorder (ADHD), and schizophrenia, tonic

inhibition has been used specifically as a treatment pathway [13,33,34]. Thus, tonic inhibition may be another causative pathway for bipolar mechanistically as well as a treatment pathway for cognitive deficits.

Another hallmark of mania is hyperlocomotion, yet there might not be an effect of tonic inhibition on locomotive recovery. As stated before, targeting a region of memory rather than locomotion may not yield changes in locomotion and other studies found no effect of the α5 receptors on locomotion [27]. It is important to note that other brain regions also express α5 receptors where they may contribute to motor behavior [35]. In addition, there are other α subunits of $GABA_A$ receptors that contribute to motor behavior [27]. Therefore, it will be worthwhile to investigate if 1) targeting α5 subunits in other brain regions affect locomotion and 2) if using combined approaches to target many subunits in these receptors can treat locomotion in addition to the already established cognitive treatment pathway in this proposal.

There are some limitations to keep in mind. Fatigue is a potential limitation, since a caveat to the DOW model is that the controls are likely at least slightly sleep-deprived since they might be awakened by the rotating disk at moments of rest. However, this apparatus remains the "gold standard" and the controls are not deprived enough to significantly differ from their rested wildtype counterparts [18,33]. Even though our trials are short enough to minimize the role of fatigue, it will be important to compare the performance of the control animals to naïve ones that aren't in the DOW, to make sure there isn't a large difference. Additionally, only male mice are noted in this study as a result of complications measuring tonic inhibition in females due to variable α5 subunit expression throughout their life cycles [37,38]. Thus, the study may be narrower since this study is only in male mice and future investigations are necessary to account for female α5 expression to mirror this study. Nevertheless, for a comprehensive treatment path both sexes must be analyzed in the future. Lastly, only one model of bipolar mouse line is utilized in this proposal, and it would be interesting to see if the role of α5 subunits is conserved in other models as well.

Conclusions

Bipolar disorder affects many people worldwide and while the current treatments provide some relief, there are long term side effects involved [32]. With a need for new treatment options for bipolar disorder, the proposed pathway considering α5 subunits may be a future, more targeted option [35]. This pathway has aims of treating many symptoms of bipolar disorder including cognitive deficits, with hopes of avoiding long term off-target effects due to its specificity.

List of Abbreviations Used

5-HT1A: serotonin 1A receptor subunit
α5-E125C-KI: α5-GABAR-E125C
$α5GABA_A$: α5 γ-aminobutyric acid type A receptor subunits
aCSF: artificial cerebrospinal fluid
ADHD: attention deficit hyperactivity disorder
ANOVA: analysis of variance
DOW: disk-over-water
EGFP: enhanced green fluorescent protein
GABA: γ-aminobutyric acid
$GABA_A$: γ-aminobutyric acid type A

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

The study requires review by the appropriate institution's ethics board to ensure experiments done on nonhuman animals are allowed.

Authors' Contributions

NV: independent contributor to this manuscript. Drafted the manuscript, made contributions to the design of the study, analyzed data, and gave final approval of the version to be published.

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