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RESEARCH ARTICLE

Projection of Bipolarity to Mitochondria: GABA Shunt is related with Self pathology and Medical Comorbidity in Bipolar Disorder

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ABSTRACT
The nature of the relationship with the self-object is the source of mental energy. At this point, the self is a spatiotemporal formation. The self has been found to be associated with the GAD enzyme activity responsible for GABA production at the molecular level. GABA is a metabolite of Krebs. Bipolar disorder is a biphasic state of energy dysregulation as a circadian rithms. Phasic nature of mitochondria to produce ATP may be crucial to the switching of affective states in bipolar disorder. The GABA shunt is an alternative energy production pathway that is activated in response to stress. The GABA shunt plays an important role in preventing the accumulation of reactive oxygen intermediates and cell death. On the other hand, GABA shunt impairs phosphorylation processes. Mitochondrial dysfunction is reflected in glucose, lipid and protein metabolism. A bipolar spectrum is possible at this point, including physical illnesses. A classification of mood disorders based on entropy levels is framed by medical comorbidity.

Keywords: Bipolar Disorder, Mitochondrial disfunction, GABA Shunt, Self pathology, Medical comorbidity

Introduction

In our previous studies, we examined the relationship between self-pathology and mood in healthy individuals and patients diagnosed with bipolar disorder[1,2].

The nature of the relationship with the self-object is the source of mental energy. At this point, the self is the organizer of the ego and body functions and a spatiotemporal formation. In the self pathologies, the shift in awareness between internal and external inputs is reflected in nonspecific bodily functions. Cognition is filled with increased self-focus and rumination. This situation has been associated with the deficit of inhibitory GABA in regulating excitatory cell input and output and local cell cycles. With flumazenil PET, response to internal and external stimuli was found to be correlated with a decrease in GABA receptor binding in the medial PFC[3]. In addition, combined EEG and MRI and alpha spectral power density were found to correlate with pregenual ACC glutamate levels[4]. The self has been found to be associated with the GAD enzyme activity responsible for GABA production at the molecular level. GABA is a metabolite of Krebs.

Bipolar disorder is a biphasic state of energy dysregulation as a circadian rithms. Phasic nature of mitochondria to produce ATP may be crucial to the switching of affective states in bipolar disorder. Allostatic load of oxidative stress and mitochondrial gene variations have a detrimental effect on mitochondrial function in bipolar patients[5]. Functional polymorphism in the mitochondrial DNA with functional effects was seen in some regions of brain.

Mitochondrial dysfunction

Mitochondrial calcium stimulated oxidative phosphorylation. Increased levels of calcium increase the activity of pyruvate dehydrogenase (PDH) leading to increased rate of ATP synthesis in mitochondria independent of mitochondrial membrane potential[6]. Calcium binds directly to cytochrome C oxidase that acts as the rate limiting enzyme in the mitochondrial electron transporte chain, and relieves this inhibition effectively bypassing feedback mechanism, allowing increased ATP production even in the presence of high ATP concentration. Elevated levels of calcium seen in some mania could initiative for the higher level of mitochondrial respiration is also seen in depression[1].

At this point to be remember calcium levels influence the activity of the circadian clock and levels of circadian clock gen outputs[7]. Of the first consideration the circadian system of bipolar patients differs in episodes of mania and depression[8]. Circadian activity is governed a tightly self-regulated oscillatory rhythm in the expression of circadian controlled gene. But circadian regulation of interconnected translation transcriptional feedback loops has proven to be deceptive. Since this is the way it is fidelity and plasticity of the circadian clock is maintained by posttranslational modification of clocks proteins, the action of certain microRNAs and cyclically coordinated epigenetic regulation of clock protein transcription[9]. So dysfunctional circadian system can putative for increased ATP levels in mania.

Increased oxidative phosphorylation driven by increases in nicotinamide dinucleotide following dietary supplementation with nicotinamide riboside. There is a relationship between elevated levels of nicotinamide dinucleotide and increased ATP generation. Sirtuin-1 allows the transcription complex to modulate its own activity by controlling levels of nicotinamide dinucleotide and provides a mechanism by which the cells energy status influences the transcription of circadian controlled genes[10]. Polymorphisms in circadian clock genes could result in higher levels of nicotinamide dinucleotide production or increased sensitivity to stimulation by sirtuin. Sirtuin levels are downregulated in the depressive episode of bipolar disorder[11]. There is no evidence the status of sirtuin-1 transcription in mania, on the other hand sirtuin-1 is upregulated in an environment of increased nitrooxidative stress as in patients with mania.

Increased levels of nicotinamide dinucleotide induce elevated levels of intracellular calcium by binding with the purinergic receptor[12]. Increased levels of ATP induce the disregulation of the circadian rhythm by overactivation of the purinergic receptor. Purinergic function was found to be impaire in bipolar disorder as a contributor to increased mitochondrial activity[13]. Uric acid activates AMP activating kinase[12]. AMP activating kinase is contributors of the regulation of energy process in the cell. Increased AMP activating kinase levels exert a positive influence on ATP generation by regulating the activity of sirtuin-1. AMP activating kinase directly regulates the function of the circadian genes. At this point it is related regulators of endocrine and metabolic rhythms[14-18]. AMP activating kinase is also upregulated by elevated proinflammatory cytokines in bipolar disorder.

There is some evidence that activity of GSK-3 lead to antagonistic effect on the output of the circadian clock[19]. Several intracellular signalling cascades

and neurotransmitter systems regulate the activity of GSK-3 which is related bipolar disorder[14-18]. The interactivity between the dopamine and glutamate at the postsynaptic space is regulated by GSK-3 via phosphorylation of postsynaptic density proteins[20]. These proteins are calcium ion dependent. Elevated levels of dopamine and glutamate with calcium would be expected to impaire oxidative phosphorylation and to initiate cellular apoptosis. Their cytotoxic effects can be counterbalanced with exaggerated upregulation of antiapoptotic proteins and stimulate the generation of ATP while protecting mitochondria from oxidative damage and death. Melatonin also protects the mitochondria from oxidative damage[21]. It may increase ATP generation by increasing the efficiency of the electron transport chain by limiting electron leakage and oxygen free radical production, thereby minimizing structural damage and feedback inhibition. Most of notification demonstrates the mitochondrial dysfunction with switch to glycolysis in depressive episode and euthymic state[22]. However for manic episode suggestions were increased mitochondrial respiration and ATP production. Probable mechanisms investigated for this state in this review.

GABA Shunt

Glucose and oxygen are vital for the brain. Glucose metabolism and mitochondria play a crucial role in this process, leading to an increase in reactive oxygen species. Hexokinase (HK) is a key enzyme in glucose metabolism and is linked to brain mitochondrial redox modulation by recycling ADP for oxidative phosphorylation. Although glucose and GABA metabolisms are inherently linked, their interactions that coordinate mitochondrial function are not fully understood[23]. Tiagabine and vigabatrin block the effects of the GABA shunt on oxidative phosphorylation-induced HK activity. This is evidence that glucose phosphorylation is linked to GABA and Krebs cycle reactions.

The γ-aminobutyric acid (GABA) shunt constitutes a conserved metabolic pathway in many organisms that produces nicotinamide adenine dinucleotide phosphate (NADPH) and regulates the stress response. The GABA shunt is an alternative energy production pathway that is activated in response to stress. It increases levels of succinate, a Krebs cycle intermediate. This metabolic pathway, which skips two steps of the tricarboxylic acid cycle, is also present in prokaryotes and eukaryotes[24]. In plants, this pathway consists of the calcium/calmodulin-regulated cytosolic enzyme glutamate decarboxylase and the mitochondrial enzymes GABA transaminase and succinic-semialdehyde dehydrogenase (SSADH). The activity of the GABA shunt in plants increases rapidly in response to various biotic and abiotic stresses. The GABA shunt plays an important role in preventing the accumulation of reactive oxygen intermediates and cell death.

Succinic semialdehyde dehydrogenase (SSADH) is a key enzyme in the GABA shunt that converts succinic semialdehyde (SSA) to succinate, a Krebs cycle intermediate. Lack of SSADH activity stimulates the conversion of SSA from the GABA shunt to γ-hydroxybutyrate (GHB), an alternative pathway. GHB may cause not only acute neuroprotective activities but also chronic harmful effects that can lead to cognitive impairment.

Catabolization of GABA involves transamination to succinic semialdehyde and subsequent oxidation to succinate by the concerted actions of GABA transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH), respectively. GHB is a neurotransmitter and psychoactive drug that can enter the citric acid cycle via transhydrogenation of α-ketoglutarate to SSA and D-hydroxyglutarate, a reaction catalyzed by hydroxyacid-oxoacid transhydrogenase (HOT). Here, the increase in matrix succinate concentration caused by exogenous addition of GABA, SSA, or GHB shifts the balance of the reversible reaction catalyzed by succinate-CoA ligase towards ATP (or GTP) hydrolysis, effectively reducing the substrate level. In other words, it disrupts phosphorylation[25].

Succinate levels increase during the transition from oxidative phosphorylation to glycolysis. Increased mitochondrial oxidation of succinate via succinate dehydrogenase (SDH) and elevation of mitochondrial membrane potential stimulate the production of mitochondrial reactive oxygen species (ROS). RNA sequencing shows that this combination induces a pro-inflammatory gene expression profile, while dimethyl malonate (DMM), an inhibitor of succinate oxidation, promotes an anti-inflammatory process[26]. Metabolic changes that occur upon activation of macrophages redirect mitochondria from ATP synthesis to ROS production to promote a pro-inflammatory state.

Catabolic products of the GABA shunt support metabolic homeostasis. Glutamate, rather than succinic semialdehyde, explains the metabolic phenotype of GABA-T mutants. Altered tricarboxylic acid cycle intermediates of GABA-T mutants were observed to exhibit a general impairment in bioenergetics as measured by NAD(+)/NADH and ATP levels.

In this study developed defective herpes simplex virus 1 (HSV-1) vectors based on amplicon plasmids with a replication-deficient mutant, aiding the transfer of the glutamic acid decarboxylase (GAD67) or beta-galactosidase (beta-gal) gene[27]. While GAD67 protein was detected immunochemically, GAD67 activity was detected enzymatically or by GABA release in virus-producing and non-producing cell lines. Infection with amplicon vectors expressing GAD67 increased resistance to H_2O_2. This protection was associated with increased energy metabolism, as indicated by ATP level. It involved GABA shunting, as demonstrated by the decrease in ATP levels seen in the presence of gamma-vinyl GABA (GVG), a specific GABA-T inhibitor. The level of glutathione (GSH), which requires ATP for its synthesis, was increased by the GAD67 transgene. The activity of glucose-6-phosphate dehydrogenase, which is involved in maintaining NADPH that can be used to replenish the GSH pool, was increased by infection with amplicon vectors. Thus, replication-deficient HSV-1 and the GAD67 transgene have complementary neuroprotective effects. Infection with GAD67-expressing amplicon vectors can protect undifferentiated cortical neurons from oxidative stress-mediated glutamate toxicity.

Conclusion

Allostatic load of oxidative stress and mitochondrial gene variations have a detrimental effect on mitochondrial function in bipolar patients. Functional polymorphism in the mitochondrial DNA with functional effects was seen in some regions of brain. The GABA shunt is activated as a stress response. It is activated to clear free radicals that accumulate and are harmful to the cell. But this has a price. Phosphorylation processes suffer from this.

Mitochondrial dysfunction is a precursor to medical comorbidity in bipolar disorder. In our classification based on the energy levels we calculate on EEG, medical comorbidity divides mood disorders into three groups[17]: i) Reactive and cyclic mood disorder accompanied by metabolic syndrome components, proliferative cancers of the breast, prostate and gastrointestinal system, ii) Comorbid anxiety accompanied by allergic and autoimmune diseases. - mood disorder, iii) mood disorder with psychotic findings accompanied by epilepsy, leukemia, lymphoma and pathologies of the hypopituitary-gonadal axis. The first two groups are characterized by hypothalamopituitary-adrenal and hypothalamopituitary-thyroid axis pathologies, respectively.

References

1. Kesebir S. Two new biomarkers and Mood Disorders: Bipolar Self, Bipolar EEG. *Med Res Arch*. 2024;12:e5071.
2. Karova ZY, Kesebir S. Is there a relationship between self and mood ? *Bipolar Disord*. 2021;23:68.
3. Northoff G, Sibille E. Cortical GABA neurons and self-focus in depression: a model linking cellular, biochemical and neural network findings. *Mol Psychiatry*. 2014;19:959.
4. Bai Y, Nakao T, Xu J, et al. Resting state glutamate predicts elevated pre-stimulus alpha during self-relatedness: A combined EEG-MRS study on "rest-self overlap". *Soc Neurosci*. 2016;11:249-263.
5. Kato T. Mitochondrial dysfunction and bipolar disorder. *Curr TOP Behav Neurosci*. 2011;5: 187-200.
6. Arnold S, Kadenbach B. Cell Respiration is Controlled by ATP, an Allosteric Inhibitor of Cytochrome-c Oxidase. *Eur J Biochem*. 1997;249: 350-354.
7. Lundkvist G. A, Kwak Y, Davis EK, et al. Calcium Flux Is Required for Circadian Rhythm Generation in Mammalian Pacemaker Neurons. *J Neurosci*. 2005;25:7682-7686.
8. Novakova M, Prasko J, Latalova K, et al. The circadian system of patients with bipolar disorder differs in episodes of mania and depression. *Bipolar Disord*. 2014;17: 303-314.
9. Masri S, Zocchi L, Katada S, et al. The circadian clock transcriptional complex: metabolic feedback intersects with epigenetic control. *Ann N Y Acad Sci*. 2012;1264: 103-109.
10. Asher G, Gatfield D, Stratmann M, et al. SIRT1 Regulates Circadian Clock Gene Expression through PER2 Deacetylation. *Cell*. 2008;134:317-328.
11. Abe N, Uchida S, Otsuki K, et al. Altered sirtuin deacetylase gene expression in Patients with a mood disorder. *J Psychiatric Res*. 2011;45:1106-1112.
12. Zhang Y, Yamamoto T, Hisatome I, et al. Uric acid induces oxidative stress and growth inhibition by activating adenosine monophosphateactivated protein kinase and 3 extra cellular signalregulated kinase signal pathways in pancreatic β cells. *Mol Cell Endocrinol*. 2013;375:89-96.
13. Kesebir S, Tatlidil Yaylaci E, Suner O, et al. Uric acid levels may be a biological marker for the differentiation of unipolar and bipolar disorder: the role of affective temperament. *J Affect Disord*. 2014;165:131-134.
14. Kesebir S. Metabolic syndrome and childhood trauma: Also comorbidity and complication in mood disorder. *World J Clin Cases*. 2014;16: 332-337.
15. Kesebir S. Epigenetics of Metabolic Syndrome as a Mood Disorder. *J Clin Med Res*. 2018;10(6):453-460. doi: 10.14740/jocmr3389w.
16. Kesebir S, Koc MI, Yosmaoglu A. Bipolar Spectrum Disorder May Be Associated With Family History of Diseases. *J Clin Med Res*. 2020;12(4):251-254.
17. Kesebir S, Demirer RM. Reclassification of Mood Disorders with Comorbid Medical Diseases based on Sinai-Ruelle-Bowen/ SRB Entropy Measures. *Medical Research Archives*. 2023;11(12).
18. Kesebir S, HaJiyeva G, Guliyev E, et al. Bipolarity Trait Index. *Bipolar Disord*. 2022;24:47-48.
19. Besing R, Paul J, Hablitz L, et al. Circadian Rhythmicity of Active GSK3 Isoforms Modulates Molecular Clock Gene Rhythms in the Suprachiasmatic Nucleus. *J Biol Rhythms*. 2015;30:155-160.
20. de Bartolomeis A, Tomasetti C. Calcium-Dependent Networks in Dopamine– Glutamate Interaction: The Role of Postsynaptic Scaffolding Proteins. *Mol Neurobiol*. 2012;46:275-296.
21. Lopez A, Garcia JA, Escames G, et al. Melatonin protects the mitochondria from oxidative damage reducing oxygen consumption, membrane potential, and superoxide anion production. *J Pineal Res*. 2009;46:188–198.
22. Morris G, Berk M. The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC Med*. 2015;1:13:68.
23. Cavalcanti-de-Albuquerque JP, de-Souza-Ferreira E, de Carvalho DP, et al. Coupling of GABA Metabolism to Mitochondrial Glucose Phosphorylation. *Neurochem Res*. 2022;47(2):470-480. doi: 10.1007/s11064-021-03463-2.
24. Bouché N, Fait A, Bouchez D, et al. Mitochondrial succinic-semialdehyde dehydrogenase of the gamma-aminobutyrate shunt is required to restrict levels of reactive oxygen intermediates in plants. *Proc Natl Acad Sci U S A*. 2003;27;100(11):6843-8. doi: 10.1073/pnas.1037532100.
25. Ravasz D, Kacso G, Fodor V, et al. Catabolism of GABA, succinic semialdehyde or gamma-hydroxybutyrate through the GABA shunt impair mitochondrial substrate-level phosphorylation. *Neurochem Int*. 2017;109:41-53. doi: 10.1016/j.neuint.2017.03.008.

26. Salminen A, Jouhten P, Sarajärvi T, et al. Hypoxia and GABA shunt activation in the pathogenesis of Alzheimer's disease. *Neurochem Int.* 2016;92:13-24. doi: 10.1016/j.neuint.2015.11.005.
27. Lamigeon C, Prod'Hon C, De Frias V, et al. Enhancement of neuronal protection from oxidative stress by glutamic acid decarboxylase delivery with a defective herpes simplex virus vector. *Exp Neurol.* 2003;184(1):381-92. doi: 10.1016/s0014-4886(03)00400-x.