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Letter to Editor Open Access

Projection of Biphasic State to Mitochondria

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Letter to Editor

Bipolar disorder is a biphasic state of energy dysregulation as 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 [1]. Functional polymorphism in the mitochondrial DNA with functional effects was seen in some regions of brain.

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 [2]. 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 [3]. Of the first consideration the circadian system of bipolar patients differs in episodes of mania and depression [4]. 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 [5]. 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 [6]. 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 [7]. 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 [8]. 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 [9]. Uric acid activates AMP activating kinase [8]. 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 Supplementary files 2 metabolic rhythms [10]. 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 [11]. Several intracellular signalling cascades and neurotransmitter systems regulate the activity of GSK-3 which is related bipolar disorder [10]. The interactivity between the dopamine and glutamate at the postsynaptic space is regulated by GSK-3 via phosphorylation of postsynaptic density proteins [12]. 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 [13]. 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 [14]. However for manic episode suggestions were increased mitochondrial respiration and ATP production. Probable mechanisms investigated for this state in this letter.

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