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The Inhibition of ATP Production by Lithium: A Preliminary Study in Whole Mitochondria from Rat Brain and a Putative Model for Bipolar Disorder

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Abstract

Lithium is a common and effective treatment and prophylaxis for manic episodes associated with Bipolar Disorder (BD). However, lithium treatments also involve numerous side effects that include nausea, lethargy and renal toxicity. Unfortunately, the development of novel agents to replace lithium in the treatment of BD is impeded because lithium's pharmacological mode of action is unknown. Here, a novel theory on lithium's mode of action and BD pathology is developed. Briefly, in response to intracellular proton level fluctuations, lithium ions directly inhibit the excess flow of protons through complex V (ATP synthase) of the oxidative phosphorylation pathway. This, thereby, limits ATP synthesis, reducing biological energy to the cell and body, and provides lithium's anti-manic effect. Preliminary experiments found that lactic acid can modulate ATP synthesis and that lithium concentrations in the therapeutic range (at < 1.0 mM concentrations) inhibit ATP production dose dependently in whole mitochondria extracted from rat brains. Despite this theory not receiving a full scientific investigation, a putative model is developed and the potential ramifications of this model are discussed to raise awareness of another possibility for lithium's mode of action so that it can receive further consideration by the neuroscience and medical communities. Investigation of this model may lead to the development of new and better mood stabilizing therapeutics as well as lead to a better understanding of the pathology of complex neural and mental disorders.

ABBREVIATIONS

BD: Bipolar Disorder; ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; IMPase: Inositol Monophosphatase; GSK-3β: Glycogen Synthase Kinase 3β; PAP: Phospho adenosine phosphate; EGTA: Ethylene Glycol Tetra acetic Acid; HEPES:4-(2-Hydroxyethyl)-1-Piperazine-Ethane-Sulfonic Acid; EDTA: Ethylene Diaminetetraacetic Acid; DTT: Dithiothreitol; CF(0)F(1): Chloroplast F_0-Proton Pore Subunit F_1-Catalytic Subunit

BACKGROUND

Lithium, a small positively charged cation (atomic number 3), is a common and effective treatment and prophylaxis of manic episodes in Bipolar Disorder (BD) [1-3]. Unfortunately, the clinical use of lithium is not always beneficial because there are numerous side effects associated with its use [3-5] and many patients discontinue their treatments, which can lead to the recurrence of mania [6,7]. Furthermore, the therapeutic range (0.6 – 1.0 mM blood serum concentration) and toxic levels (> 1.5 mM blood serum concentration) of lithium are separated by a small margin [8], which limits its efficacy. Ultimately, it would be best to replace lithium with a better and more suitable long term mood stabilizing treatment for BD. However, no definitive treatment is known and various other non-specific neurological agents are often used to manage bipolar symptoms [2,9]. Attempts to develop novel treatments are hindered by the complexity of the disorder, as well as the fact that lithium's mechanism of action remains unknown.

Lithium has been found to directly inhibit three main catalytic enzymes [10]: Inositol Monophosphatase (IMPase)

[11], Glycogen Synthase Kinase 3β (GSK-3β) [12,13] and Phosphoadenosinephosphate (PAP) Phosphatase [14,15]. These enzymes have diverse biological functions that create a web of down-stream fluctuations that are difficult to map and further complicate the understanding of lithium's mode of action. Most investigations on the potential role of lithium's action use chronic genetic evaluations and post-mortem studies to identify hopeful gene targets [16-21], but no definitive mechanism has been described. This confusion is added to by the nature of the disorder, which appears to manifest as acute energetic fluxes between extreme highs and lows that are observed clinically as manic and depressive episodes.

A number of observations have lead to the investigation of energy metabolism in the mitochondria and of mitochondrial dysfunction as the localized malfunction within individual cells in BP patients [22,23]. These observations include increased levels of oxidative damage [17,24,25], many altered mRNA levels for energy metabolism genes (from glycolytic genes to electron transport genes) in post-mortem brains from bipolar patients [26-28] and decreased pH levels in post-mortem [29] and living bipolar patients [30-32]. However, it is still not clear how these observations express the manic or depressive symptoms, nor how lithium provides its anti-manic effect.

Yet, careful consideration of these findings presented a novel and unique solution to the question of lithium's mode of action. In particular, the alteration in pH suggested potential fluctuations in proton concentrations in living cells in bipolar patients. Although, it is not explicitly known what impact proton accumulation in the cytoplasm might have, a general interpretation is that the potential difference across the inner mitochondrial membrane (~180 mV) [33] would create a greater driving force and increased influx of protons through Complex V (adenosine triphosphate (ATP) synthase) of the oxidative phosphorylation pathway. Thereby, increasing mitochondrial matrix and cellular levels of ATP, leading to more biological energy available in the cell and body, which potentially engages the manic phase of BD. Interestingly, a recent study has found lower intracellular pH levels and adenosine diphosphate (ADP) levels in the anterior cingulate cortex of manic BD adolescents [32]. A finding that is consistent with this notion of increased ATP synthesis during mania.

With this in consideration, it might not be a coincidence that lithium provides an anti-manic effect. If lithium, a very small positive cation, is added into this system, it is expected to follow the same electrochemical driving force that pulls protons towards the mitochondrial matrix. However, in comparison to the size of a proton, the lithium ion would be too large to pass through the proton-exchange mechanism of the ATP synthase complex and thus limit the flow of protons by blocking the proton pore, inhibiting ATP production and potentially causing the aforementioned anti-manic effect seen in bipolar patients. This postulation provides a novel and simple identity to the mechanism of action of lithium that is conceptually parallel to the clinical phenotype of lithium treatments. Interestingly, a study in March 2009 proposed such a mechanism in which the H^+-ATP synthase from chloroplasts CF(0)F(1) was tested against concentration gradients of Na^+ and Li^+. While, the sodium gradient was found to drive ATP synthesis, lithium was found to inhibit the enzymatic activity of ATP synthase by presumably blocking the pore of CF(0) [34].

The postulation and hypothesis presented here are intended to raise awareness of a novel mechanism for understanding lithium's mode of action such that it may receive better consideration by the neuroscience community, as well as the appropriate critical review. Although, the work presented contains only preliminary experiments and preliminary results without statistical analysis and no follow-up work was ever performed, the presentation of the experimentation is intended to provide a starting point for the research community going forward in the hopes that the ideas presented will open new doors in neuroscience as well as lead to the development of better therapeutics for BD and other mental health disorders.

METHODS

An ATP-coupled luciferase assay on whole mitochondria extracted from rat brain was used to analyze ATP production. The assay and extraction were designed as previously described [35].

Mitochondrial Extraction

Three young *ad-libitum* fed male sprague-daley rats (Charles River Laboratories, Willmington, MA, USA; < 4 months of age),in accordance with the Canadian Council on Animal Care guidelines for the care and use of laboratory animals, were used in this study. On separate experiment days, individual rats were anesthetized with 20 % urethane (2 mL) and then sacrificed by decapitation. The cranium was opened and the brains removed. The forebrain and midbrain were homogenized together on ice in an isotonic mitochondrial extraction buffer ((IMEB): 210 mM Mannitol, 70 mM Sucrose, 1 mM EGTA, 0.1% Bovine Serum Albumin, 10mM mM HEPES buffer, pH 7.5) with a standard glass-glass dounce homogenizer. Mitochondria were isolated through 3 steps of centrifugation at 4°C (1: 800 g for 10 min to collect supernatant; 2: 11,000 g for 10 min; 3: the pellet was re-suspended in IMEB and centrifugation was repeated, 11,000 g for 10 min. The pellet was re-suspended in 10 volumes of IMEB containing 1X protease inhibitor cocktail (Actif Motif, Carlsberg, Cal, USA). Freshly extracted mitochondria were kept on ice and assayed on the same day to ensure mitochondria viability. Mitochondrial protein concentration was determined by the Bradford method [36].

ATP production assay

A basic ATP luciferase kit (Molecular Probes, Invitrogen, USA) was used to perform a standard assay containing 25 mM Tricine buffer, pH 7.8, 5 mM $MgSO_4$, 0.1 mM EDTA, 0.1 mM sodium azide, 1 mM DTT, 0.5 mM D-luciferin, 1.25 ug/mL firefly luciferase and 2.5 mM ADP (substrate to ATP synthase; substrate concentration of maximal ATP production activity; purchased from Invitrogen). The luminescence change as a measure of ATP production was measured in a luminometer with multi-well plate reading capabilities (Tecan Safire Instrument, Tecan, Mannedorf, Switzerland). Assays were carried out at 28°C in a total reaction volume of 100 µL. Data were normalized to the average control because the background luminescence increased overtime (period of hours) at which the measurements were taken.

Preliminary Experiments

(1) To demonstrate whether proton concentrations modulate ATP synthesis, a concentration gradient (0 – 8 mM) of 10:1 ratio of lactate: pyruvate was added to assays with rat brain mitochondria as this mixture has been shown to decrease mitochondrial matrix pH [37]. (2) To determine whether lithium ions modulate ATP synthesis, a concentration gradient (0 – 8 mM) LiCl was added to assays with rat brain mitochondria. (3) To assess ionic influence on mitochondrial activity, a preliminary test was performed during assay development with a NaCl gradient (0 – 2mM) as a control.

RESULTS

The rate of luminescence/ATP production by rat brain mitochondria increased with the acid gradient (0.1 mM-1 mM lactate:pyruvate), suggesting that pH changes might modulate ATP synthesis (Figure 1A). However, at higher lactate concentrations (> 2 mM) the rate diminished from its peak. It is not clear whether this was due to a decrease in mitochondria function at low pH, indirect inhibition by lactate or simply quenching of the luminescent signal with a higher proton concentration.

The inclusion of lithium into the ATP assay demonstrated that lithium had a dose dependent inhibiting effect on rat brain mitochondrial ATP production (Figure 1B), even at very low concentrations (< 0.5mM).Sodium chloride gradients on the other hand, had little effect of ATP production (Figure 1C). The results presented here must be considered preliminary and warrant further re-evaluation; no statistical analysis was performed, nor should significance be reported here.

DISCUSSION

Lithium poses great challenges to neuroscience as a whole and, more specifically, to the treatment of bipolar patients, who would benefit from a deeper understanding of its mechanism of action by the medical community. A first challenge is that not all patients respond to lithium [38]. Second, the medical community appears to be divided into two camps: (1) lithium as a chronic neuroprotective agent [16-21] and (2) lithium as an acute anti-manic agent [1-4,39]. Third, lithium's therapeutic and toxic ranges border on a close line (~1 mM in the blood) [8] leading to side effects [3-5] and discontinuance by patients [6,7]. It is difficult to account for such diverse understanding other than to suggest that maybe not all bipolar symptoms result from similar molecular causes. Yet, multiple studies have reported decreased intracellular pH levels in the living brain of BD patients and in post mortem tissue investigations [29-32], suggesting that its relevance may need to be re-evaluated.

In this preliminary study, this relevance was investigated with a quick ATP-coupled luciferase assay of whole mitochondria from rat brain. It was performed in a multi-well plate luminometer to provide a first assessment of the hypothesis that lithium mediates the anti-manic effect through the inhibition of ATP synthesis. Although, one advantage of the system was that it controlled multiple tests simultaneously, the approach had considerable disadvantages. For example, the small volume exaggerated any minute pipetting error and there was no way to ensure the sample was mixed thoroughly. Nonetheless, it would have been more ideal to perform experimentation that repeated Chen *et al*'s procedure [34] and reconstituted mammalian brain ATP-Synthase in proteoliposomes to investigate lithium's role directly. However, resources to perform this work have not been available. As such, this report was drafted to raise awareness of

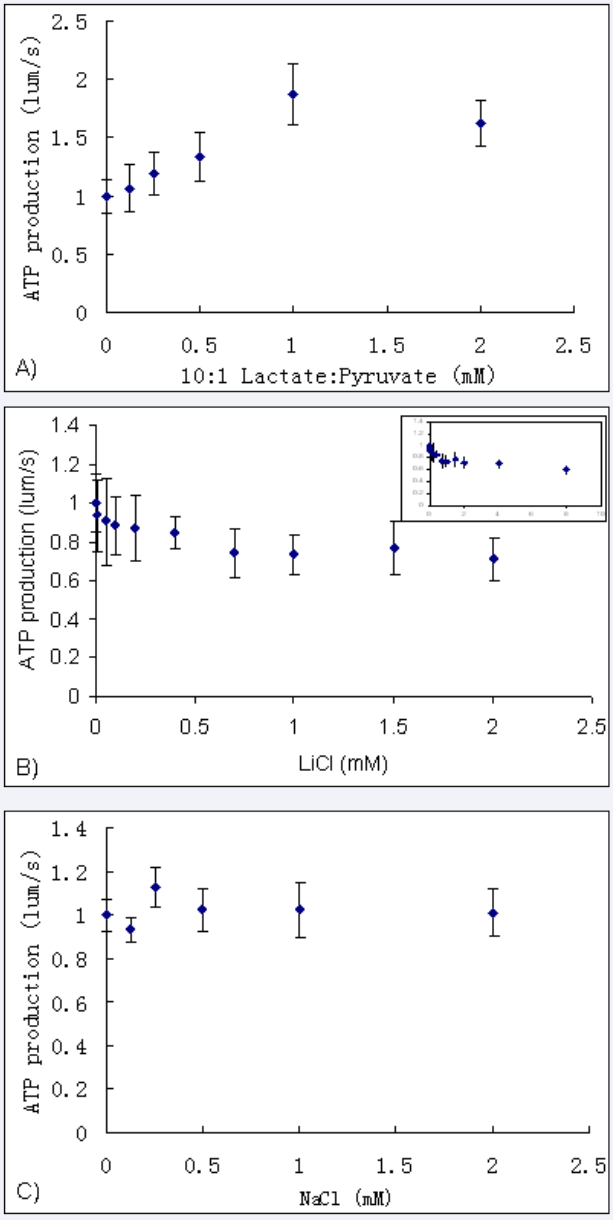

Figure 1 ATP production vs. increasing concentrations of lactic acid, lithium chloride and sodium chloride. Whole mitochondria extracted from rat brain were assayed for ATP production using a luciferase-coupled assay with an increasing concentration gradient of (A) 10:1 lactate: pyruvate (pKa ~ 3.8), 0 - 2 mM; (B) Lithium Chloride, 0 – 2 mM (Inset image is expanded data for 0 – 8 mM); (C) Sodium Chloride, 0 – 2 mM. Rate of luminescence change was measured over a 1 - 1.5 minute interval. Protein concentration in the assays were ~15 ug/100 uL assay (A) and ~16ug/100uL (B&C). The assay was repeated 3 times in (A) and 4 times in (B&C) with the same mitochondria samples. Data points are normalized to controls and expressed as the mean +/- the standard error of the mean in arbitrary luminescence units/unit time.

another possibility for lithium's mode of action, not to provide conclusive data.

Although the relationship between pH, lithium, ATP synthesis, and mitochondrial function or dysfunction is likely complex, the preliminary work presented here and the direct evidence from plant chloroplast ATP synthase [34] suggests the potential inhibition of ATP synthesis by lithium ions may constitute a mechanism of action for lithium's anti-manic effect. The proton concentration variation in the lactic acid dependent assay presented here suggests that increasing proton numbers will drive ATP synthesis in mitochondria. While, the inhibition of ATP synthesis by lithium at the sub-therapeutic concentrations in the preliminary mitochondrial assays implies a physiological relevance, especially in consideration that intracellular pH fluctuation may be an important facet of mania [32]. This relevance is also supported by findings that similar cations like sodium do not negatively modulate ATP synthesis in whole mitochondria, nor in purified extractions of chloroplast ATP synthase) [34], suggesting that this type of direct inhibition is specific to the small lithium cation.

It is important to state that the preliminary results presented here do not conclusively confirm the inhibition of ATP synthesis by lithium in the mammalian brain. Nonetheless, the findings from plant derived purified ATP synthase in proteoliposomes [34] and the supportive, albeit preliminary, evidence presented here in whole mitochondria from rat brain allow for the development of a new therapeutic model of lithium's mode of action and for a new model into the pathology of BD. Briefly, this BD model derives from the decreased intracellular pH level in the BD brain [32] and a prolonged flow of excessive protons into the mitochondrial matrix. Although the potential effects of this expectation are not explicitly known at this time, it potentially leads to the depletion of the electronegative pull into the mitochondria causing a potential crash of mitochondrial function. This crash may contribute to mitochondrial or cellular death and potentially account for depression in BD. This notion is compatible with the lower levels of ATP and high-energy phosphate metabolites observed in depression patients [40,41], the alteration in energy metabolism gene expression found in post-mortem bipolar patient [22], and the prevalence of oxidative damage in the bipolar brain as a result of dysfunctional mitochondrial energy metabolism. This link between oxidative damage, mitochondrial dysfunction, apoptosis and Bipolar depression has already been suggested [25]. However, the characteristic manic/depressive cycling of BD requires a model and a new investigation that includes both sides of the coin. This model might account for this cycling with the inclusion of protons and ATP synthesis. Prior to or following a depressive episode, mitochondria maybe under duress from a pre-existing metabolic pH problem, leading to uncontrolled energy (ATP) production, creating a new acute manic event. One that lithium helps to prevent by inhibiting ATP synthesis. For example, lithium in this model may simply provide prophylaxis by protecting against uncontrolled proton flow into the mitochondria such that when a patient discontinues therapeutic use, the patient experiences a new manic event. In any regard, this putative model needs considerable investigation to validate its role in BD and the inhibition of ATP synthesis by lithium needs to be reevaluated with direct ATP synthesis kinetics with purified proteins from mammalian brain tissue in order to confirm this pharmacological mode of action for lithium's anti-manic effect (Figure 2).

Moreover, this postulation might explain other lithium related phenomenon related to BD treatment and research. First, lithium is known to attenuate ouabain induced mania [42-44], where ouabain is a known inhibitor of the Na^+/K^+ ATP dependent pump [45,46] that induces manic or hyper motive behavior in animal [43,47]. It is plausible that lithium's potential inhibition of ATP synthesis simply counteracts the presence of excess ATP in neurons that has not been utilized by a major ATP depleting enzyme required to maintain cellular homeostasis that is being inhibited by ouabain. Potentially, it is this excess ATP that drives the observed mania in this model, as ATP is essential to many neuronal functions such as intracellular proton excretion [48], forming proton gradients for neurotransmitter vesicle packing [49] and vesicle transport [50].

Second, the inhibition of ATP synthesis by lithium may also explain the small range between lithium's therapeutic and toxic levels, given that ATP is essential to many biological functions. In consideration of lithium's specific toxicity to kidneys [5], it is also plausible to rationalize the need of the body to flush out lithium ions due to the potential impairment of such a critical enzymatic step; that as the kidneys concentrate the lithium ions during the excretion process, the kidneys might be uniquely susceptible to the adverse effects of lithium ions. This might lead to renal impairments through ATP supply shortages that add stress to the functioning kidneys.

Further research is required to confirm the potential roles of lithium based inhibition of ATP synthesis in ouabain induced animals and in renal or other toxicity. However, the parallels between the molecular hypothesis presented here and clinical phenotype of lithium treatment make it pertinent to discuss these related implications of lithium treatments. Especially because lithium at the right concentration remains the main prophylactic against manic episodes [2,3] and is used chronically, despite its toxicity, with considerable side-effects that include nausea and lethargy [3-5].

It is well established that lithium has a neuro-protective effect [51], which has led to lithium being investigated as a therapeutic agent for use in many disorders linked to oxidative damage, such as Amylotrophic Lateral Schlerosis (ALS) [57] and Alzheimer's Disease (AD) [58]. It is possible that the potential

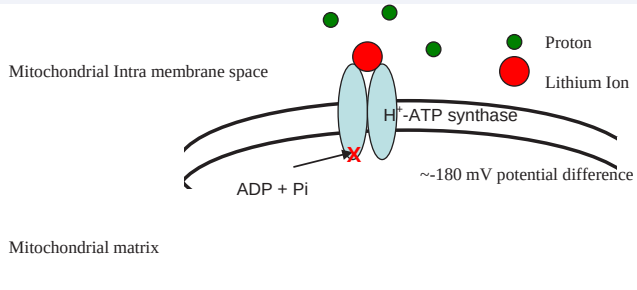

Figure 1 Schematic representation of the potential Lithium blockage of Complex V.

inhibition and regulation of proton flow through ATP synthase by lithium may protect mitochondrial function and may limit any corresponding oxidative damage, potentially contributing to the observed attenuation of oxidative damage by lithium [15,22,44], in addition to the neuro-protection provided by lithium through specific genetic modulations that counteract oxidative damage [15-20,54]. The possibility that both mechanisms work in concert to synergistically protect cells from oxidative damage has not been considered, despite providing an advantage over considering specific genetic modulations alone to explain lithium's pharmacological effects.

There is a striking difference between neurological disorders with strong physical correlates, such as ALS or AD, and disorders like BD, where the physical correlations have not been well defined. Yet, investigations into their etiologies, treatments and outcome are focused on similar biological functions and the most common investigations of lithium's mode of action and the potential causes of BD revolve around chronic down-stream genetic modulations [25-30], which are based on lithium's inhibitory effects on GSK-3β [12,13], IMP [11] and, more recently, PAP phosphatase [14,15], with regards to oxidative damage in the BD brain. This further complicates the role of lithium in the treatment of BD because Bipolar disorder is a mental disorder with few established physical correlates and the scientific gap between genetics and mental faculties is a tumultuous ocean of speculation. As such, it remains unclear how physiologically relevant findings like oxidative stress and genetic modulation relate directly to the clinical phenotypes of BD and similar disorders of the mind.

We intuitively teach ourselves that water is the essential component and ultimate balance to life. For a disorder like BD, where homeostatic balance is compromised in a manner that manifests in relatively opposite clinical phenotypes (mania and depression), it might not be prudent that main stream research focuses predominantly on genetic modulation and oxidative damage. It is likely that these two phenomena associated with bipolar disorder (pH imbalance and oxidative damage) are intricately linked. However, this relationship is rarely considered in bipolar research, despite water imbalance garnering some review in relation to mental health [55]. The pH decrease in BD [29-32] may be a key component of the disorder and it has not received a fair scientific inquiry in relation to BD pathology. As such, the cause of this pH imbalance remains unknown. It has been suggested to arise from increased anaerobic metabolism needed to compensate for impaired aerobic respiration due to mitochondrial dysfunction [28], but more work is needed to fully elucidate the cause and role of pH in BD. Nonetheless, this aspect of BD and the potential inhibition of ATP synthesis by lithium in response to lower intracellular pH levels, has, in concept, interesting parallels between both physiology and behavior in BD. This similarity suggests that further investigation of the role of lithium in ATP synthesis will lead to many new insights about the brain, in addition to evaluating a new pharmacological model for lithium's anti-manic effect.

In summary, there is a strong impetus for further external evaluation and validation of the putative model that low intracellular pH drives mania through ATP production and that lithium provides its anti-manic effect by directly inhibiting ATP synthesis, despite current experimental work being insufficient to scientifically establish the role of pH and lithium in BD. This impetus includes an evolutionary precedence for the inhibition of ATP synthesis by lithium [34] and decreased intracellular pH in BD [22]. This essay also presented potential descriptions and preliminary outcomes in regards to lithium, pH and BD, such that this prospect may receive better consideration and critique by the neuroscience and medical communities. Investigation into this mechanism of action for lithium may provide new insights into the cause of mania, the use of lithium as an anti-manic agent and the future treatment of BD. Such insights might also lead to better diagnostic and less toxic therapeutic approaches for BD. Ultimately, future research into this question will help to solidify our understanding of mitochondrial health and its relevance to mental disorders such that manic-depressive symptoms can be better alleviated in the 1-2% of the global population that suffer with Bipolar disorder [56-58].

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