Review article
Ανασκόπηση

Is impulsivity in part a lithium deficiency state?

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Lithium mechanisms of action are related to the function of many enzymes, hormones, vitamins, and growth factors. In humans, lithium treatment has been associated with humoral and structural evidence of neuroprotection, such as increased expression of anti-apoptotic genes, inhibition of cellular oxidative stress, synthesis of brain-derived neurotrophic factor, cortical thickening, increased grey matter density, and hippocampal enlargement. Lithium, in pharmacological doses, has been used successfully in treating bipolar disorders, and has been shown to decrease suicidality and violent crime in this situation. The guidelines of major psychiatric association name lithium as a first-line therapy for bipolar disorder. From the other hand, impulsivity is a core feature of bipolar disorder. Increased levels of this dimensional trait are present not only during acute phases of the illness but also during euthymia. Increased impulsivity worsens clinical prognosis of bipolar disorder due to its association with several severity indices, such as substance abuse or dependence, suicidal behavior, and poorer functional outcome. A wide range of intracellular responses may be secondary to the inhibition of glycogen synthase kinase-3 beta (GSK3β) by lithium, while genetic variability at GSK3β gene was found to be associated with increased impulsivity in bipolar patients. Although impulsivity has been traditionally linked to dysregulation of serotonergic and dopaminergic systems, some authors have proposed that lithium could reduce impulsivity levels by means of its capacity to regulate the aforementioned neurotransmitter systems. Moreover, lithium in trace amounts, as occurs in drinking water, has been inversely related to suicidal mortality, aggression and homicidal violence. These findings pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks. It seems also that in the competition for survival, those entities that best minimized lithium toxicity and maximized the benefits of lithium action had an edge in the competition to survive and reproduce. Finally, lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus. Evidence from both basic and clinical researches support that lithium may decrease impulsivity and may at least partially, exert its antisuicidal effect via reinforcing “top-down brakes” of impulsive action. Considering the research data, we may suggest that even natural lithium level intake can influence impulsivity, a possible core factor that mediate to the manifestation of both suicidality and aggressiveness, or even criminality. Moreover, we may suggest that a lithium deficiency state may precipitate these situations.

Key words: Lithium, impulsivity, suicide, bipolar disorder.

Lithium and neuroscience

Lithium is ubiquitous in the environment and probably an essential trace nutrient. Interesting questions about lithium abound at all levels of science, ranging from the microscopic to the cosmic. As a natural trace element, lithium is washed out by rain from rocks and from the soil, dissolving in ground water and reaching the food chain via drinking water. Lithium plays an important role in embryogenesis and biochemical mechanisms of action are related to the function of many enzymes, hormones, vitamins, and growth factors. Lithium displaces magnesium ions and inhibits at least 10 cellular targets, all of which are components of intracellular signalling pathways. Lithium effects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase.[1] Lithium is considered as the most effective mood-stabilizer used to treat bipolar disorder.[2] Lithium blood concentration varies normally from .00001 to .00009 moles/liter, while the therapeutic target range for bipolar is .0005 to .001 moles/liter, which is about 100 times the high end of the normal range.

Epidemiological studies in bipolar patients revealed that continued lithium treatment was associated with reduction of the rate of dementia to the same level as that for general population, and that effects were not found in anticonvulsants, antidepressants, or antipsychotics, suggesting a specific effect of lithium.[3] Neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment, while chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein.[4] Lithium treatment may yield disease-modifying effects in Alzheimer Disease, both by the specific modification of its pathophysiology via inhibition of the overactive enzyme glycogen synthase kinase-3 (GSK-3), and by the unspecific provision of neurotrophic and neuroprotective support.[5]

Helbich et al[6] (2013) have found some interesting associations, investigating the relationship between suicide mortality, lithium levels in drinking water, and the altitude above sea level. These new research and methodological approaches contribute to the induction of new avenues in the collaboration between biology, chemistry and psychiatry, by exploring the association between lithium content in drinking water and mental health, and especially suicide mortality, as well as violent or impulsive crime.[7]

Low lithium intakes and suicide mortality

Some ecological studies have shown an association between low lithium intakes from water supplies and suicide, as well as homicide rate. Schrauzer & Shrestha (1990),[8] using data from 27 Texas counties for the period 1978–1987, found that the incidence rates of suicide, homicide, and rape were significantly higher in counties whose drinking water supplies contain little or no lithium than in counties with water lithium levels ranging from 70–170 μg/L. Ohgami et al (2009)[9] examined lithium levels in tap water in the 18 municipalities of Oita prefecture in Japan, in relation to the suicide standardised mortality ratio in each municipality. They found that lithium levels were significantly and negatively associated with suicide standardised mortality ratio averages for 2002–2006 and suggested that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population. Kapusta et al (2011)[10] evaluated the association between local lithium levels in drinking water and suicide mortality at district level in Austria. The overall suicide rate as well as the suicide mortality ratio were inversely associated with lithium levels in drinking water, and remained significant after sensitivity analyses and adjustment for socioeconomic factors.

Similarly, Blüml et al (2013)[11] evaluated the association between lithium levels in the public water supply and county-based suicide rates in 226 Texas counties, with a state-wide sample of 3123 lithium measurements from the public water supply. The findings provided evidence that higher lithium levels in the public drinking water are associated with lower suicide rates. However, Kabacs et al (2011),[12] measuring lithium levels in tap water in the 47 subdivisions of the East of England and correlating these with the suicide standardised mortality ratio in each subdivision, found no association between lithium in drinking water and suicide rates across the East

of England for the period 2006–2008. A recent study showed that lithium levels in drinking water were significantly and inversely associated with male but not total or female suicide standardized mortality ratios, in 274 municipalities of Kyushu Island in Japan.[13] Another recent research by Liaugaudaite et al (2017) showed also that the higher levels of lithium in public drinking water systems from 9 cities of Lithuania were associated with lower suicide rates in men.[14]

These findings pose the question of whether the prospect of adding lithium to drinking water is realistic, weighing the benefits and potential risks, and the bulk of evidence may suggests that the optimum level of lithium intake is more than most people get from food and drinking water. Considering that research, in his paper titled "Is violence in part a lithium deficiency state?", Goldstein (2016)[15] suggested: "In order to ensure adequate dietary intakes of elemental lithium daily for the purpose of decreasing aggression and violence, we propose considering the fortification of cereal grain products with lithium and also the addition of lithium to vitamin preparations for adults".

The dimensional trait of impulsivity

Impulsivity is a core feature of bipolar disorder. Increased levels of this dimensional trait are present not only during acute phases of the illness but also during euthymia.[16,17] It has been widely demonstrated that increased impulsivity worsens clinical prognosis of bipolar disorder due to its association with several severity indices, such as substance abuse or dependence,[18] suicidal behavior,[16] presence of axis I and/or II comorbidities,[19] and poorer functional outcome.[20] Impulsivity is considered to be constituted by three different factors: attentional-cognitive, motor and non-planning impulsivity, at the Barratt Impulsiveness Scale,[21] which has been suggested to present differential predictive validity for a variety of relevant psychiatric or behavioral outcomes.[22]

Impulsivity has been shown to be heritable.[23–24] The presence of increased levels of impulsivity in bipolar patients has been consistently associated with chronicity, a more unstable course of the illness, characterized by an increased number of episodes, an earlier onset and the presence of depressive predominant polarity, a poorer compliance and a correlation between higher impulsivity and the severity of the suicidal attempt.[26] Moreover, research data indicate that there are common pathways between aggression and impulsivity.[27]

Lithium and impulsivity

Following the above studies which investigated the relation between low lithium intakes from water supplies and suicide, we evaluated the association between lithium levels in the public water supply and prefecture-based suicide rates in Greece. Analysis was conducted with respect to lithium levels in 149 samples from 34, out of 52, prefectures of Greece. The average lithium level was 11.10 μg/L (range 0.1 to 121 μg/L). The results indicated a tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water.[28] Extending this study, we found a tendency of lower mean number of homicides in the prefectures with high levels of lithium in drinking water.[29] Considering these results, we suggested that natural lithium level intake may influence impulsiveness, a possible core factor that mediate to the manifestation of both suicidality and aggressiveness, or even criminality. Helbich et al (2013),[6] concluded to similar suggestions, after investigating the relation between suicide mortality and lithium levels in drinking water.

An association between genetic variability at glycogen synthetase kinase-3β (GSK3β) emergence of bipolar disorder and response to lithium has been well rehearsed.[30,31] Based on findings that lithium inhibits both GSK3 isoenzymes, Jiménez et al (2014),[32] analyzed the potential impact of genetic variants located at the GSK3α and GSK3β genes on impulsivity levels, and they found that genetic variability at GSK3β gene was associated with increased impulsivity in bipolar patients. Lithium, which is considered as one of the most effective mood-stabilizers used to treat bipolar disorder, decreases levels of impulsivity as measured by different outcome measures not only in bipolar patients, but also in other impulse control disorders.[33–37] Although impulsivity has been traditionally linked to dysregulation of serotonergic and dopaminergic systems, some authors have proposed that lithium could reduce impulsivity levels by means of its capacity to regulate the aforementioned neurotransmitter sys-

tems.[38] Lithium inhibits GSK3β isoenzyme[39] which in turn is known to act as a mediator of serotonergic function.[40] The inhibition of GSK3 has been suggested to play a key role of the therapeutic action of most of the "gold-standard" pharmacological agents used to treat mood disorders.[39]

Lithium may have superior antisuicidal effects relative to other mood stabilizers.[37,41,42] A recent meta-analysis[43] in 48 randomized control trials comparing lithium with placebo or active drugs in long term treatment for mood disorders, concluded that lithium is an effective treatment for reducing the risk of suicide in people with mood disorders, and the authors suggested that impulsivity might be a mechanism mediating the antisuicidal effect. John Cade (1949),[44] the Australian psychiatrist credited with discovering the effects of lithium carbonate as a mood stabilizer in the treatment of bipolar disorder, reported the original paper with the title "Lithium salts in the treatment of psychotic excitement". We can suggest that Cade's concept of excitement may fit better with that concept of impulsiveness.[1] Considering all the above data, we may suggest that even low lithium intakes can influence impulsivity, a core factor that mediate to the manifestation of both suicidality and aggressiveness, or even criminality. Moreover, we may suggest that a lithium deficiency state may precipitate these situations.

Many clinical neuroscience data is in accordance with the above suggestion. The pharmacologic mechanisms of action of lithium and amphetamine seem to be directly opposite and lithium could be prophylactic for cases of amphetamine abuse.[45] With regard to the mechanism, taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus,[46] it seems likely that lithium may at least partially exert its antisuicidal effect via reinforcing "top-down brakes" of impulsive action. Since lithium has been shown also to increase the volume and function of the hippocampus,[47] antisuicidal, antiaggressive and antiimpulsive effects of lithium may rely on a stable balance between the "top-down brakes" and the "bottom-up drive".[4] In a recent study, Tobe et al (2017),[48] using human-induced pluripotent stem cells (hiPSCs) from patients with bipolar disorder responsive to lithium, found that lithium alters the phosphorylation state of collapsin response mediator protein-2 (CRMP2). The authors suggested that the "lithium response pathway" in bipolar patients governs CRMP2's phosphorylation, which regulates cytoskeletal organization, particularly in spines, modulating neural networks. Finally, other mechanisms acting in parallel, like the initial lithium induced hypothyroidism may help to rearrange and normalize thyroid hormone secretion in the long-term therapy, acting possibly through an adaptive thyroid system resetting, which may results in a correction of an isolated CNS hypothyroidism.[49]

Μπορεί η παρορμητικότητα να υποδηλώνει εν μέρει μία κατάσταση έλλειψης λιθίου;

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Οι μηχανισμοί δράσης του λιθίου σχετίζονται με τη λειτουργία πολλών ενζύμων, ορμονών, βιταμινών και παραγόντων ανάπτυξης. Στους ανθρώπους η θεραπεία με λίθιο συνδέεται με χυμικές και δομικές ενδείξεις νευροπροστασίας, όπως αυξημένη έκφραση των αντιαποπτοτικών γονιδίων, αναστολή του οξειδωτικού κυτταρικού στρες, σύνθεση των νευροτροφικών παραγόντων, πάχυνση του φλοιού, αύξηση πυκνότητας της φαιάς ουσίας και αύξηση όγκου του ιπποκάμπου. Το λίθιο

σε φαρμακολογικές δόσεις έχει χρησιμοποιηθεί με επιτυχία στη θεραπεία της διπολικής διαταραχής και έδειξε να μειώνει την αυτοκτονικότητα και την εγκληματικότητα στα περιστατικά αυτά. Οι οδηγίες συνταγογράφησης μεγάλων οργανισμών θεωρούν το λίθιο πρώτης γραμμής θεραπεία της διπολικής διαταραχής. Από την άλλη πλευρά, η παρορμητικότητα είναι ένα πυρηνικό στοιχείο της διπολικής διαταραχής. Αυξημένα επίπεδα αυτού του διαστασιακού χαρακτηριστικού είναι παρόντα όχι μόνο στη διάρκεια των οξέων φάσεων της νόσου, αλλά και στη διάρκεια των φάσεων νορμοθυμίας. Η αυξημένη παρορμητικότητα επιδεινώνει την κλινική πρόγνωση της διπολικής διαταραχής, μέσω διάφορων συνοδών κλινικών εκδηλώσεων, όπως η εξάρτηση από ουσίες, η αυτοκτονικότητα και η πτωχή λειτουργικότητα. Ένα μεγάλο εύρος ενδοκυτταρικών απαντήσεων μπορεί να σχετίζονται με την αναστολή του GSK3β από το λίθιο, ενώ ο γενετικός πολυμορφισμός του GSK3β γονιδίου βρέθηκε να σχετίζεται με αυξημένη παρορμητικότητα στους διπολικούς ασθενείς. Αν και η παρορμητικότητα έχει παραδοσιακά συνδεθεί με ανεπαρκή ρύθμιση του σεροτονινεργικού και ντοπαμινικού συστήματος, ορισμένοι ερευνητές έχουν προτείνει ότι το λίθιο μπορεί να μειώσει τα επίπεδα παρορμητικότητας μέσα από την ιδιότητα να ρυθμίζει τα παραπάνω νευρομεταβιβαστικά συστήματα. Επιπλέον, το λίθιο σε στοιχειώδη επίπεδα, όπως συμβαίνει στο πόσιμο ύδωρ, έχει σχετιστεί αντίστροφα με την αυτοκτονικότητα, την επιθετικότητα και την εγκληματικότητα. Τα ευρήματα αυτά θέτουν το ερώτημα κατά πόσον η ενδεχόμενη πρόσθεση λιθίου στο πόσιμο ύδωρ είναι ρεαλιστική, ζυγίζοντας το όφελος και το πιθανό κόστος. Φαίνεται μάλλον ότι τα όντα εκείνα που ελαχιστοποιούν τον κίνδυνο τοξικότητας του λιθίου και μεγιστοποιούν τα οφέλη της δράσης του βγαίνουν ενισχυμένα στην επιβίωση και την αναπαραγωγή. Τέλος, βρέθηκε ότι το λίθιο αυξάνει τον όγκο του προμετωπιαίου φλοιού και του πρόσθιου πρσαγωγίου. Οι ενδείξεις τόσο από τη βασική όσο και την κλινική έρευνα υποστηρίζουν ότι το λίθιο μπορεί να μειώνει την παρορμητικότητα, ενώ μπορεί τουλάχιστον εν μέρει να έχει αντιαυτοκτονική δράση μέσα από την ενίσχυση των «από πάνω προς τα κάτω φρένων» στην παρορμητικότητα. Λαμβάνοντας υπόψη τα παραπάνω δεδομένα, μπορούμε να υποθέσουμε ότι ακόμη και τα φυσικά επίπεδα πρόσληψης λιθίου ενδέχεται να επηρεάσουν την παρορμητικότητα, έναν πυρηνικό παράγοντα που διαμεσολαβεί στην εκδήλωση τόσο της αυτοκτονικότητας όσο και της επιθετικότητας, ή ακόμη και της εγκληματικότητας. Επιπλέον, μπορούμε να υποθέσουμε ότι μια κατάσταση έλλειψης λιθίου μπορεί να προδιαθέσει σε τέτοιες καταστάσεις.

Λέξεις ευρετηρίου: Λίθιο, παρορμητικότητα, αυτοκτονίες, διπολική διαταραχή.

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