International Journal of Advanced Research and Publications
ISSN: 2456-9992

Effect Of Therapeutic Lithium Carbonate Doses On Rat Brain Content Of Mood Regulating Neurotransmitters

Abdel-Hamid, NM, El-Shaer, SS , Gad, A

Ex-Dean of Faculty of Pharmacy, Kafrelsheikh University, Egypt; Tel: +201227300491; Fax: +20473215768
E-mail: nabilmohie@yahoo.com

Biochemistry Department, Faculty of Pharmacy, A-Azhar University, Cairo, Egypt

Pharmacology Department, National Organization of Drug Control and Research, ,Giza, Egypt.

Abstract: The anti-depressant value of lithium on rat brain tissue was studied at different treatment periods to explore its impact on brain neurotransmitters related to mood disorders (dopamine and histamine) ,precursors with further highlighting on minerals implicated in their synthesis (magnesium and calcium). We examined a therapeutic dose (75 mg/kg/d) on four groups of rats, 6/each, grouped according to duration into, control group; given saline (group 1), acute study group; given single dose, left for 2 hours (group 2), sub-acute study group; given a dose each 3 days for 2 weeks (group 3) and a chronic study group; given a dose each 3 days for a month (group 4). Brain content of dopamine and histamine was significantly decreased on acute treatment, but increased for dopamine and decreased for histamine after 2 weeks while it flipped for each of them after one month of administration. Gama aminobutyrate (GABA), glycine and histidine were significantly decreased after each period of treatment while phenyl alanine was significantly decreased only after a month of treatment. These changes occurred with increased magnesium and decreased calcium brain content on both acute and sub-acute treatment. Brain content of both of them was decreased on chronic treatment. These actions reveal that lithium has a remarkable effect on brain neuronal function which probably postulates an interesting impact of lithium treatment in shifting amino acids and needed minerals in direction of improving the mood, through neurotransmission homeostasis. **List of abbreviations:** 5HT: serotonin; AA: arachidonic acid; Ach: acetylcholine; AD: Alzheimer disease; BD: bipolar disorder; BDNF: brain-derived neurotrophic factor; cAMP: cyclic adenosine monophosphate; Cdk5: cyclin-dependent kinase 5; ER: endoplasmic reticulum; GABA: gamma-Aminobutyric acid; GSK3: Glycogen synthase kinase 3; HDAC: Histone deacetylase; IL-1β**:** Interleukin 1 beta; IL-6**:** Interleukin 6; IP3: inositol 1, 4, 5-trisphosphate; NMDA: N-methyl-D-aspartic acid; PAI-1: plasminogen activatorinhibitor-1; PD: Parkinson's disease; SNc: substantianigra pars compacta; TBARS: Thiobarbituric acid reactive substances; TNF-α: Tumor necrosis factor alpha.

Key words: Lithium carbonate; Brain tissue; Bipolar Disorders; Neuroprotective; Neurotransmitters; Amino acids; Dopamine; Histamine; Magnesium, Calcium.

1. Introduction

Lithium salts have been widely used in different fields of medicine for more than sixty years, specially in psychiatry [1-5]. There have been some reports about promising outcomes concerning the possibility of its application in neurology [6, 7]. Lithium is largely known for its usage in the treatment of bipolar disease. The mechanism of lithium's mood-stabilizing activity has not been clarified, in part because lithium exerts its effects on a large scale of cellular functions: for example, it inhibits inositol production, affects the protein kinase C signaling pathway and inhibits glycogen synthase kinase 3 (GSK3) [8-10]. Moreover, various studies in cellular and animal models have demonstrated that lithium can suppress neurodegeneration resulted from different sorts of insults, such as Alzheimer disease and amyloid-ß peptide [11], glutamate excite toxicity and ischemia [12]. Consistent with its protective actions, lithium treatment enhanced Bcl-2 expression but decreased Bax and p53 expression in rat cerebellar granule cells under glutamate challenge, thus prohibiting caspase activation [13]. Acute and chronic treatment of bipolar disorder (BD) patients with lithium carbonate has been accompanied by up-regulation of particular biological cascades related to neuro-protection. Lithium treatment significantly increased plasma levels of brain-derived neuro-trophic factor (BDNF), with a motivating efficacy on response to treatment. Also, Lithium modifies other remarkable biological processes related to inflammation and oxidative stress [14], besides, lithium treatment of acute mania episodes was accompanied by a worthy reduction of pro-oxidative stress markers, that are thiobarbituric acid reactive substances (TBARS) [15]. Additionally, lithium has been proved to be engaged in remyelination and axonal regeneration [16]. BD patients who reacted with lithium treatment in a good response also had a serious reduction in plasma levels of tumor necrosis factor alpha (TNF-α); in contrast, BD patients who did not quiet respond to lithium showed a significant increase in TNF-α levels [17]. More and above that, lithium can restore the balance between the production of interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) in monocytes of bipolar patients in vitro; this effect is similar to those observed in vivo [18]. There are some other mechanisms by which lithium has been shown to act intracellularly. These include modification of cyclic adenosine monophosphate (cAMP)-mediated signal transduction [19-21]; lessening in the arachidonic acid (AA) cascade [22]; negative regulation of the Smad3/4-transcription factor and protein levels of plasminogen activator inhibitor-1 (PAI-1); and induction of neurogenesis [23]. Furthermore, lithium has been indicated to motivate the survival pathway, MEK/ERK [24]; increase transcription factor β-catenin levels [25]; and regulate autophagy via inositol inhibition and

reduction of inositol 1, 4, 5-trisphosphate (IP3) levels [26]. An Ample evidence elucidated that dysfunction of serotoninergic neurotransmission in CNS is involved in the evolution of anxiety, depression and memory disorders [27]. The impact of lithium on serotonin metabolism is established, it increases brain tryptophan, 5-HIAA and 5-HT levels, as well as increased synthesis rate of brain serotonin [28]. Lithium carbonate has been noted to alter GABA levels, possibly decreasing impulsive and aggressive behavior by increasing availability and efficacy of GABA [29]. A worthy notable that lithium affects memory by interaction with acetylcholine (Ach), N-methyl-D-aspartate (NMDA), serotonin (5HT), dopamine (DA), neurotrophic factors, prostaglandins and kinases in distinct brain areas [30]. These observations propose an influential function of lithium in synaptic plasticity and cognition tuning. Amino acids can serve as the most powerful compounds in the treatment of neurological diseases in the upcoming years. Amino acids maintain regeneration and reorganization processes of neurons [31]. Changes of these amino acids neurotransmitters have been notified in many neurological and psychiatric disorders such as depression, Alzheimer's disease, schizophrenia and epilepsy [32-36]. As an outcome of these observations, this study was conducted to clarify lithium carbonate impact on the metabolic pathways at different treatment durations and assess brain content of neurotransmitters and amino acids/neurotransmitters exchange at brain tissue, to add further explanation of neuro-protective role of therapeutic doses of lithium carbonate.

2. Materials and methods

2.1. Animals

A total of twenty four male Swiss albino rats, weighting between150-200 g each, were used in this study. The animals were purchased from Faculty of Veterinary Medicine, Zagazig University, Egypt. Animals were left for two weeks for acclimatization under standard laboratory conditions with temperature at 23±2^{o}C, and 12:12 light/dark cycle. The animals were allowed free access to food and water. The standard guidelines were used in handling the experimental animals and we complied with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2. Experimental Design

Rats were randomly classified into 4 experimental groups;
Group1: Served as control, rats received saline (1 ml; i.p.).
Group 2: Rats received single dose of lithium carbonate (75 mg/kg; i.p.), used for the study of the acute effect of lithium carbonate, then sacrificed after 2 hrs.
Group 3: Rats received lithium carbonate (75 mg/kg; i.p, sub-acute study) for two consecutive weeks.
Group 4: Rats received lithium carbonate (75 mg/kg; i.p, chronic study) for 4 weeks.
The animals treated for two weeks and one month were injected in 1st and 4th day of the week, thus the animals treated for two weeks received 5 doses and those for a month received 10 doses. The animals treated for two weeks were sacrificed on the third day of the last injection; while those treated for a month were sacrificed on the fourth day of the last injection. After scarification of rats, brains were carefully removed, blotted and chilled. The tissue content of brain neurotransmitters (dopamine and histamine), some free amino acids (ɣ- aminobutyrate, glycine, histidine; histamine precursor, phenyl alanine; dopamine precursor and tyrosine) as well as calcium and magnesium were estimated.

2.3. Chemicals

All chemicals were of analytical grade, obtained from Sigma-Aldrich, USA.

2.4. Methods

Estimation of free amino acids in brain tissue extract The extraction of free amino acids from brain tissue was made according to steps reported before [37], as follows: 1 g of brain tissue homogenate was triturated with 5 ml of 80% ethanol at 4^{o}C. The mixture was centrifuged at 3000 rpm. for 5 minutes. The clear supernatant was subjected for amino acid determination (glycine, γ-aminobutyrate, histidine, phenyl alanine and tyrosine) using amino acid auto analyzer (Technicon, Model R.120).

Estimation of Dopamine

it was estimated in brain homogenate according to the method described elsewhereSchlumpf, Lichtensteiger, Langemann, Waser and Hefti [38]. At the end of experiment rats were sacrificed, whole brain was dissected out and separated. One gm of frozen tissue was homogenized in 12ml HCl–butanol for about 1 min. The sample was then centrifuged for 10 min at 2000 rpm. An aliquot supernatant (9.6 ml) was pipetted and added to centrifuge tube containing 24 ml heptane and 3 ml0.1 M HCl. After 10 min of vigorous shaking, the tube was centrifuged under the same conditions as above in order to separate the two phases, and the overlaying organic phase was discarded. The aqueous phase (2.4 ml) was then taken for Fluormetric DA assay. All steps were carried out at 0^{o}C. Dopamine was determined spectrofluorimetrically. The fluorescent compound produced was measured by Schimadzu spectrofluormeter Rf 510, at excitation wavelength of 330 nm and emission wavelength of 375 nm.

Estimation of Histamine

One g of brain tissue was triturated with 4 ml of 20% trichloroacetic acid and the mixture was left aside for 3 hours on cold. Then the mixture was centrifuged at 3000 rpm for 10 minutes. The supernatant was separated and shaken with equal volume of ether for 3 min to remove excess trichloroacetic acid, and then the ether phase was discarded. To the aqueous phase, 1 g of ion-exchange resin was added and set aside for 10 minutes with regular shaking, then centrifuged for 5 min at 3000 rpm. and then the supernatant was separated and preserved at 4^{o}C for 5 min. Then, 0.85 ml of clear supernatant was diluted with equal volume of 1 N HCl. Histamine was assessed spectrofluorimetrically using Schimadzu spectrofluormeter Rf 510, at excitation wavelength of 360 nm and emission wavelength of 450 nm[39].

Estimation of calcium and magnesium

We made many dilutions to fit the scale of the atomic absorption spectrophotometer (Schmidazu). So, 250 mg of brain tissues were homogenized with 12 ml of 0.1 N HCl and 4 ml of 10% trichloroacetic acid, the mixture was centrifuged at 2000 rpm for 3 min, then 0.1 ml of clear supernatant was diluted to 10 ml by 0.1 N HCl. Firstly, magnesium was determined. These samples were used for measuring calcium after addition of 1 ml lanthanum chloride 1% to each tube (using magnesium lamp)Parker, Humoller and Mahler [40]

2.5. Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the University of Al-Azhar Research Committee (UARC), which are in accordance with the Helsinki declaration 2013; saved in the committee archive at its turn and date.

2.6. Statistical analysis

The statistical analysis of data was done using Graph Pad Prism 5 (Graph pad Software, San Diego California, USA). The results were expressed as means ± S.E.M. differences between the mean values for individual groups were assessed by one way ANOVA.

3. Results

Variations in dopamine content after lithium carbonate treatments After two hours of lithium administration to rats, dopamine content was reduced down. Administration of lithium to rats for two weeks produced a slight but significant (P< 0.05) increase in brain dopamine content to 0.94±0.02ug/g tissue. While after a month of treatment, the mean value of dopamine was significantly decreased (Figure 1). Variations in histamine content after lithium carbonate treatments After two hours of lithium administration to rats, histamine content was slightly reduced. Administration of lithium to rats for two weeks produced a significant decrease (P< 0.001) in brain histamine content. However, after a month of treatment with lithium carbonate, the mean value of histamine was significantly increased (Figure 2). Variations in magnesium content after lithium carbonate treatments Lithium carbonate administration caused a significant increase in magnesium content after two hours and after two weeks. However after a month of administration of lithium carbonate, magnesium content was slightly reduced to (Figure 1). Variations in calcium content after lithium carbonate treatments Lithium carbonate administration caused a significant decrease in brain calcium content after two hours and after two weeks, as well as after a month of administration of lithium carbonate (Figure 2). Variations in studied amino acids content after lithium carbonate treatments A significant decrease in brain content of ɣ-aminobutyrate (GABA) and histidine (histamine precursor) was observed throughout the three time periods (p<0.001), as well as, the neuroinhibitory amino acid, glycine was significantly decreased till reached the least values on longer treatment (one month) while phenyl alanine (dopamine precursor) was significantly decreased only after a month of treatment and tyrosine showed no significant decrease throughout the three periods (Figure 3).

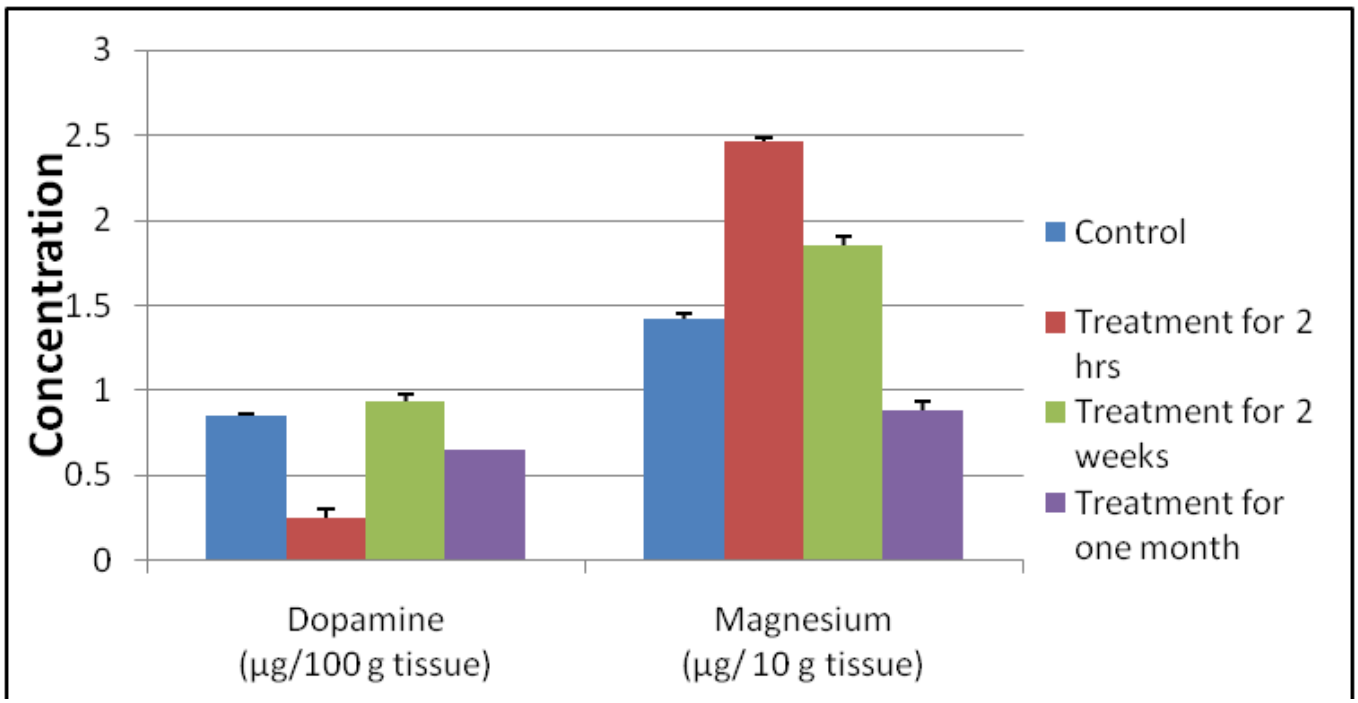

Fig (1): *The effect of lithium carbonate therapeutic dose (75 mg/kg) on dopamine and magnesium contents in rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at P < 0.05*).*

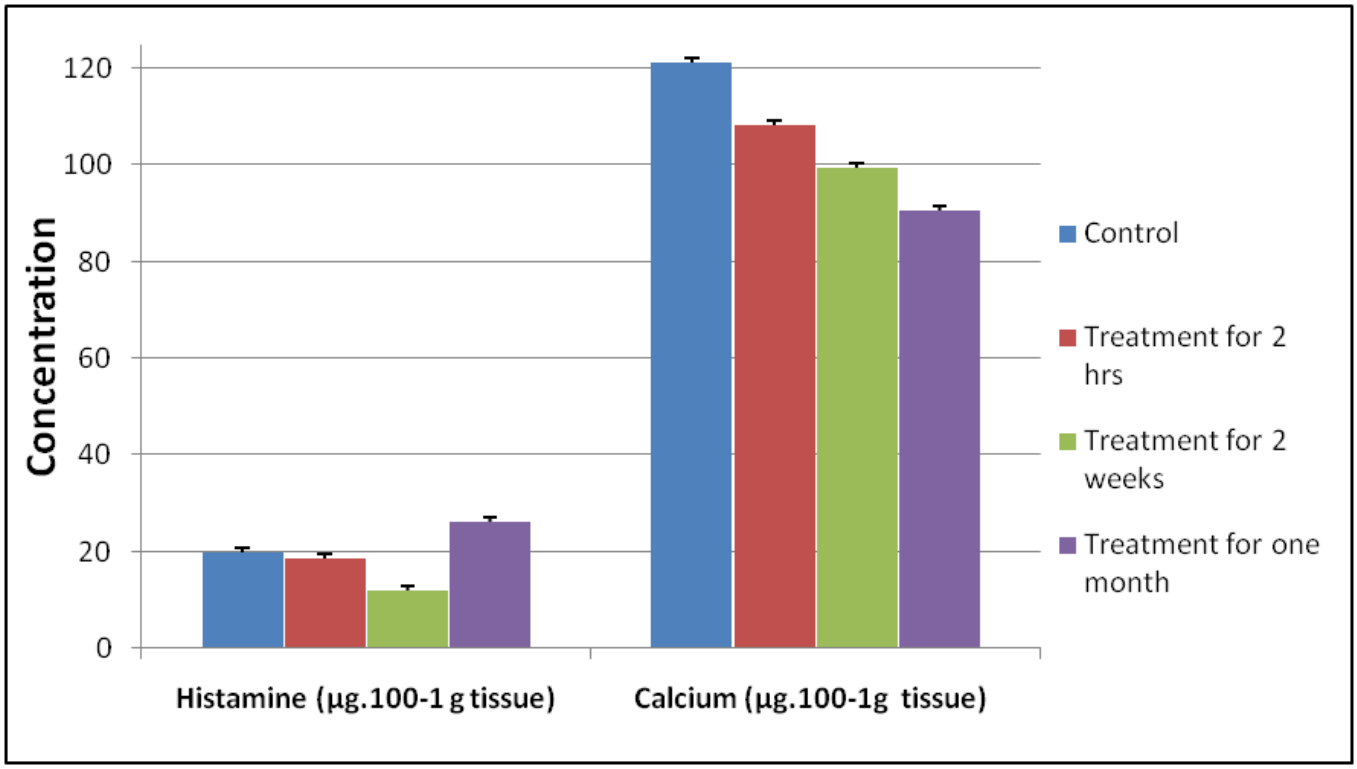

Fig (2): *The effect of lithium carbonate therapeutic dose (75 mg/kg) on histamine and calcium contents in rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at P < 0.05*).*

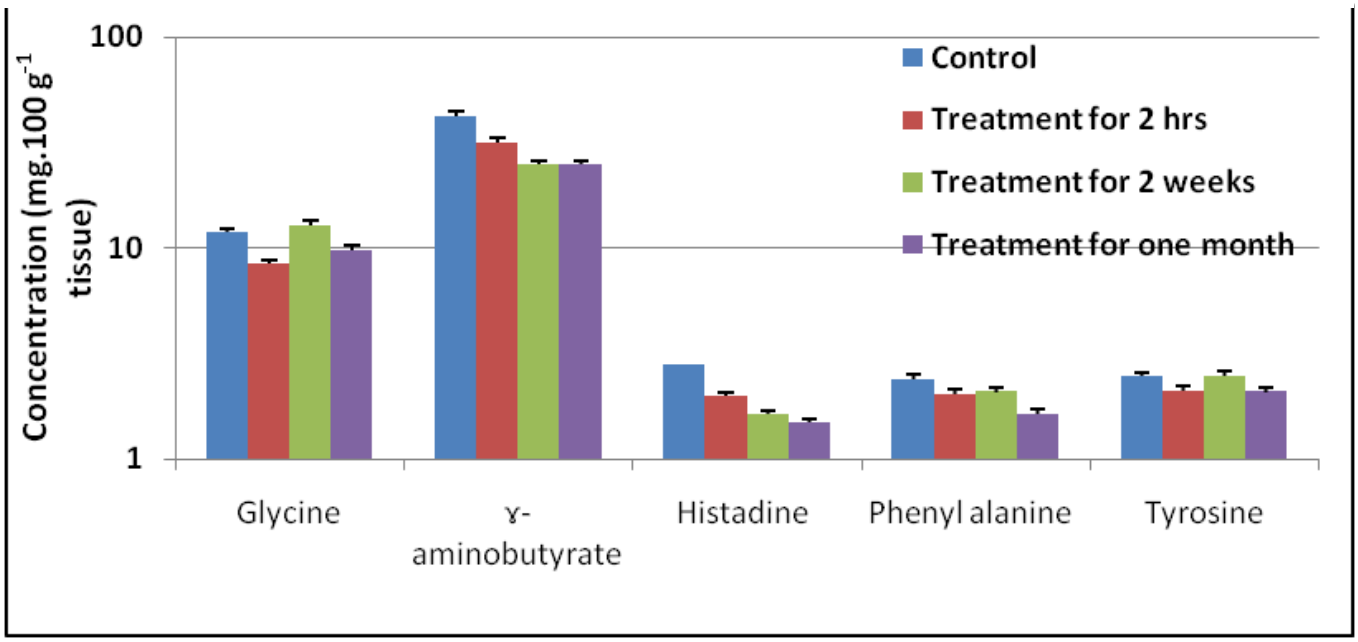

Fig (3): *The effect of lithium carbonate therapeutic dose (75 mg/kg) on glycine, γ-aminobutyrate, histidine, phenylalanine and tyrosine contents in rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at P < 0.05*).*

4. Discussion

The treatment with therapeutic doses of lithium carbonate (75 mg/kg, i.p) caused a significant increase in dopamine content after two weeks. This finding indicated that lithium possibly modulated the function and expression of transcription, factor activator protein 1 (*AP-1*) in the rats [41]. It was reported that ithium influenced extracellular concentration of dopamine in rat brain, where a decrease in the dopamine concentration in prefrontal cortex [42] and an increase in striatum [43] after the intragastric administration of lithium for two weeks. Reduction of dopamine turnover might have a role in blocking, delaying, or reducing the intensity of the switch process. Lithium mediates glycogen synthase kinase-3b (GSK-3b) inhibition, which may be related to neuroprotective effects against glutamate induced toxicity. Reportedly, the co-

treatment of lithium and histone deacetylase (HDAC) inhibitors gives a synergistic neuroprotective effect, suggesting the GSK-3b pathway as a common target for the therapeutic effect of lithium [23, 44]. The influence of lithium on histamine content could refer to the importance of histamine as a chemical neurotransmitter in brain where the actions of neuronal histamine are mediated through G-protein-coupled H1-H4 receptors [45]. The significant reduction of brain histamine contents , in this study, upon lithium treatment for two hours as well as two weeks may be considered as one of the factors which finally leads to inhibition of adenyl cyclase that probably activated by endogenous histamine. Like the dysregulation of dopamine, dysregulation of histamine levels in the brain may be another unifying factor in the pathogenesis of several diseases [46]. Histamine can selectively damage dopaminergic neurons of the substantia nigra pars compacta (SNc), leading to the increased inflammation that is characteristic for parkinson's disease (PD) pathology [47]. Administration of an irreversible inhibitor of histamine synthesis to a PD rat model produced serious protection against neuronal loss [48]. Histamine hypermetabolism may participate in PD pathophysiology by inhibiting dopamine activity: in a PD rat model, a selective H3 receptor agonist reduced dopamine release in the striatum [49]. Taken together, these findings signalize that exaggerated histamine metabolism may promote PD onset and/or progression, probably by disturbing dopamine signaling, whereas deceased histamine metabolism may exert a protective effect. In the present work, it was important to study the effect of lithium on brain content of different free amino acids because some are mood effective neurotransmitters or precursors for neurotransmitters. In addition, lithium has been shown to alter some neurotransmitter systems (e.g., norepinephrine, dopamine, acetylcholine, endorphins, GABA, substance P) [50]. The current study detected a significant decrease in brain content of GABA throughout the three treatment periods. Also, dopamine was significantly decreased after both acute and chronic treatment periods while glycine was significantly decreased on chronic treatment. These observations were consistent with some previous reports [51] stated that lithium reduces excitatory dopamine and glutamate contents in brain tissue. Moreover, lithium has been manifested to increase GABA turnover in mouse and rat brain [52]. Add to that, an experimental study has indicated that when dopamine re-uptake in the brain is inhibited, dopamine levels increase subsequent to lithium withdrawal and remain elevated for 3 days in comparison with levels in rats that continued receiving lithium [53]. The decrease in GABA and glycine during the different periods of administration indicated that lithium treatment decreases the formation of glycine and GABA, by inhibition of phosphate–dependent glutaminase [54, 55]. The current work showed that histidine and phenyl alanine brain contents were significantly decreased but tyrosine was insignificantly decreased allover treatment periods. These findings demonstrate that, in addition to a possible activation of incorporation of amino acids into polypeptides, lithium administration activates conversion of these three amino acids into active biogenic amines, as neurotransmitters, through hydroxylation [56-58]. The significant decrease in histidine content especially after one month of treatment could be parallel with increased content of histamine that indicates a possible activation of histamine synthesis in the brain, by activating histidine decarboxylae [59, 60]. The acute treatment of lithium caused a significant increase in magnesium content after two hours and also after two weeks of administration to rats; however there was a significant reduction in calcium content. Mg^{2+} and Li^{+} ions have been found to compete for binding-site of some enzymes [61]. Low serum Mg^{2+} levels are associated with several neurological diseases such as migraine, depression, epilepsy and Alzheimer disease (AD) [62-65]. The negative relationships between calcium and lithium were reported. In ovariectomized rats fed zinc-deficient diet, markedly enhanced lithium in bone was associated with a remarkable calcium decline [66]. A case report study concluded that in a lithium-treated patient, a decrease in Ca^{2+} was found [67]. Calcium cytotoxicity has been approved for about 35 years ago. There are some theories elucidate the mechanism of excitotoxicity of Ca^{2+}, and all of them emphasize the higher than given threshold cytoplasmatic calcium level as a fundamental factor which enters the cell into the apoptotic pathway [68]. The elevated Ca^{2+} level within the brain tissue in Se treated animals may propose the higher potential for excitotoxicity development; however, this observation needs further studies on cellular level. Lithium actions on the phosphatidylinositol (PI) signaling pathway, for example [69], leads to a reduction in levels of inositol-1,4,5, triphosphate (IP3), which considered as an essential stimulator for intracellular calcium levels [70]. IP3 typically mediates calcium release from the endoplasmic reticulum (ER), the primary site for protein synthesis, folding, trafficking, with additional roles in calcium signaling regulation [71]. Therefore, Lithium's reduction of IP3 levels inhibits calcium release from the ER, with effects on neuronal functioning [72]; this involves reduction in the activity of the calcium-dependent protein calpain and calpain-mediated activation of pro-apoptotic cyclin-dependent kinase 5 (Cdk5), leading to reduced cellular death [51].

Conclusion

Lithium carbonate has a serious role in managing BD, apparently, through conversion of some amino acids into their analogical stimulatory neurotransmitters on both acute and chronic treatments, in addition to handling the level of inhibitory amino acids as GABA and glycine in mood equilibrium trend, controlling neuro-transmission and tissue stabilization.

Ethical approval and consent to participate: All procedures performed in this study were in accordance with the ethical standards of the Al-Azhar University Research Committee and with the Helsinki declaration; no formal ethical review was required.

- **Consent for publication:** Not applicable
- **Availability of data and material:** All data generated or analyzed during this study are included in this article
- **Competing interests:** "The authors declare that they have no competing interests"

- **Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
- **Authors' contributions:** All authors read and approved the final manuscript.

Author Profile

- **Name : Nabil Mohie Abdel–Hamid.**
- **Current Position :** Professor of Cancer Biology at Department of Biochemistry, Ex- and First Dean and Founder of Faculty of Pharmacy, Kafrelsheikh University, Egypt.
- **National and International Memberships:**
- **Member of:** The Higher Consulting Organization of Egyptian Scientists Council.
- **Deputy of Director of:** The Egyptian Association of Cancer Research.
- **Member in:** The Arab Evaluators for Scientific Degree Promotions.
- **Member in:** The Egyptian Evaluators for Scientific Degree Promotions.

- **Research Interest:** Cancer Biology, Principal Instructor and interested in Hepatocellular Carcinoma Research(Both Early Detection, Looking for New Sensitive and Specific Markers and Therapeutic Perusal), as New Trends in Management of Hepatocellular Carcinoma, Including Chemo and Radio Sensitization to Cancer Therapy.

References:

[1] M. Ahmad, Y. Elnakady, M. Farooq, M. Wadaan, Lithium induced toxicity in rats: blood serum chemistry, antioxidative enzymes in red blood cells and histopathological studies, Biological and Pharmaceutical Bulletin, 34 (2011) 272-277.

[2] A. Albayrak, Z. Halici, B. Polat, E. Karakus, E. Cadirci, Y. Bayir, S. Kunak, S.S. Karcioglu, S. Yigit, D. Unal, Protective effects of lithium: a new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis, International immunopharmacology, 16 (2013) 35-40.

[3] U. Banerjee, A. Dasgupta, J.K. Rout, O.P. Singh, Effects of lithium therapy on Na+–K+-ATPase activity and lipid peroxidation in bipolar disorder, Progress in Neuro-Psychopharmacology and Biological Psychiatry, 37 (2012) 56-61.

[4] M. Bauer, M. Adli, R. Ricken, E. Severus, M. Pilhatsch, Role of lithium augmentation in the management of major depressive disorder, CNS drugs, 28 (2014) 331-342.

[5] K. Scheuch, M. Höltje, H. Budde, M. Lautenschlager, A. Heinz, G. Ahnert-Hilger, J. Priller, Lithium modulates tryptophan hydroxylase 2 gene expression and serotonin release in primary cultures of serotonergic raphe neurons, Brain research, 1307 (2010) 14-21.

[6] A. Camins, E. Verdaguer, F. Junyent, M. Yeste- Velasco, C. Pelegrí, J. Vilaplana, M. Pallás, Potential mechanisms involved in the prevention of neurodegenerative diseases by lithium, CNS neuroscience & therapeutics, 15 (2009) 333-344.

[7] A. Ozkul, A. Sair, A. Akyol, C. Yenisey, T. Dost, C. Tataroglu, Effects of Lithium and Lamotrigine on Oxidative–Nitrosative Stress and Spatial Learning Deficit After Global Cerebral Ischemia, Neurochemical research, 39 (2014) 853-861.

[8] G. Chen, M.I. Masana, H.K. Manji, Lithium regulates PKC- mediated intracellular cross- talk and gene expression in the CNS in vivo, Bipolar disorders, 2 (2000) 217-236.

[9] R.S. Jope, Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes, Trends in pharmacological sciences, 24 (2003) 441-443.

[10] H.R. Pilcher, Drug research: the ups and downs of lithium, Nature, 425 (2003) 118-120.

[11] C.J. Phiel, C.A. Wilson, V.M.-Y. Lee, P.S. Klein, GSK-3α regulates production of Alzheimer's disease amyloid-β peptides, Nature, 423 (2003) 435-439.

[12] D.M. Chuang, R.W. Chen, E. Chalecka- Franaszek, M. Ren, R. Hashimoto, V. Senatorov, H. Kanai, C. Hough, T. Hiroi, P. Leeds, Neuroprotective effects of lithium in cultured cells and animal models of diseases, Bipolar disorders, 4 (2002) 129-136.

[13] R.-W. Chen, D.-M. Chuang, Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression A prominent role in neuroprotection against excitotoxicity, Journal of Biological Chemistry, 274 (1999) 6039-6042.

[14] J.K. Rybakowski, A. Suwalska, Excellent lithium responders have normal cognitive functions and plasma BDNF levels, International Journal of Neuropsychopharmacology, 13 (2010) 617-622.

[15] R. Machado- Vieira, H.K. Manji, C.A. Zarate Jr, The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis, Bipolar disorders, 11 (2009) 92-109.

[16] J. Makoukji, M. Belle, D. Meffre, R. Stassart, J. Grenier, R. Fledrich, C. Fonte, J. Branchu, M. Goulard, C. de Waele, Lithium enhances remyelination of peripheral nerves, Proceedings of the National Academy of Sciences, 109 (2012) 3973-3978.

[17] S. Guloksuz, K. Altinbas, E.A. Cetin, G. Kenis, S.B. Gazioglu, G. Deniz, E.T. Oral, J. van Os, Evidence

for an association between tumor necrosis factor-alpha levels and lithium response, Journal of affective disorders, 143 (2012) 148-152.

[18] E.M. Knijff, M. Nadine Breunis, R.W. Kupka, H.J. De Wit, C. Ruwhof, G.W. Akkerhuis, W.A. Nolen, H.A. Drexhage, An imbalance in the production of IL- 1β and IL- 6 by monocytes of bipolar patients: restoration by lithium treatment, Bipolar disorders, 9 (2007) 743-753.

[19] H. Einat, P. Yuan, T.D. Gould, J. Li, J. Du, L. Zhang, H.K. Manji, G. Chen, The role of the extracellular signal-regulated kinase signaling pathway in mood modulation, Journal of Neuroscience, 23 (2003) 7311-7316.

[20] T.D. Gould, G. Chen, H.K. Manji, Mood stabilizer psychopharmacology, Clinical neuroscience research, 2 (2002) 193-212.

[21] R.S. Jope, A bimodal model of the mechanism of action of lithium, Molecular psychiatry, 4 (1999) 21-25.

[22] S.I. Rapoport, F. Bosetti, Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder?, Archives of General Psychiatry, 59 (2002) 592-596.

[23] R. Hashimoto, N. Takei, K. Shimazu, L. Christ, B. Lu, D.-M. Chuang, Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity, Neuropharmacology, 43 (2002) 1173-1179.

[24] M.-H. Liang, J.R. Wendland, D.-M. Chuang, Lithium inhibits Smad3/4 transactivation via increased CREB activity induced by enhanced PKA and AKT signaling, Molecular and Cellular Neuroscience, 37 (2008) 440-453.

[25] T.D. Gould, G. Chen, H.K. Manji, In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3, Neuropsychopharmacology, 29 (2004) 32.

[26] D.J. Klionsky, K. Abdelmohsen, A. Abe, M.J. Abedin, H. Abeliovich, A. Acevedo Arozena, H. Adachi, C.M. Adams, P.D. Adams, K. Adeli, Guidelines for the use and interpretation of assays for monitoring autophagy, Autophagy, 12 (2016) 1-222.

[27] M. Banasr, G. Chowdhury, R. Terwilliger, S. Newton, R. Duman, K. Behar, G. Sanacora, Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole, Molecular psychiatry, 15 (2010) 501-511.

[28] A. Serretti, R. Lilli, L. Mandelli, C. Lorenzi, E. Smeraldi, Serotonin transporter gene associated with lithium prophylaxis in mood disorders, The pharmacogenomics journal, 1 (2001) 71-77.

[29] T. Sakai, A. Oshima, Y. Nozaki, I. Ida, C. Haga, H. Akiyama, Y. Nakazato, M. Mikuni, Changes in density of calcium- binding- protein- immunoreactive GABAergic neurons in prefrontal cortex in schizophrenia and bipolar disorder, Neuropathology, 28 (2008) 143-150.

[30] M.H. Karimfar, K. Tabrizian, K. Azami, A. Hosseini-Sharifabad, A. Hoseini, M. Pourghorban, M. Aghsami, S. Gholizadeh, M. Abdollahi, A. Roghani, Time course effects of lithium administration on spatial memory acquisition and cholinergic marker expression in rats, DARU Journal of Pharmaceutical Sciences, 17 (2015) 113-123.

[31] I. Morales, L. Guzman-Martinez, C. Cerda-Troncoso, G.A. Farias, R.B. Maccioni, Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches, Front Cell Neurosci, 8 (2014) 112.

[32] N.B. Farber, J.W. Newcomer, J.W. Olney, The glutamate synapse in neuropsychiatric disorders. Focus on schizophrenia and Alzheimer's disease, Prog Brain Res, 116 (1998) 421-437.

[33] Y.V. Tcherkas, L.A. Kartsova, I.N. Krasnova, Analysis of amino acids in human serum by isocratic reversed-phase high-performance liquid chromatography with electrochemical detection, Journal of Chromatography A, 913 (2001) 303-308.

[34] T. Sumiyoshi, A.E. Anil, D. Jin, K. Jayathilake, M. Lee, H.Y. Meltzer, Plasma glycine and serine levels in schizophrenia compared to normal controls and major depression: relation to negative symptoms, Int J Neuropsychopharmacol, 7 (2004) 1-8.

[35] K. Hashimoto, A. Sawa, M. Iyo, Increased levels of glutamate in brains from patients with mood disorders, Biol Psychiatry, 62 (2007) 1310-1316.

[36] O.Y. Nagasawa M, Kurata K, Otsuka T, Yoshida J, Tomonaga S, Furuse M. Furuse,, Hypothesis with abnormal amino acid metabolism in depression and stress vulnerability in Wistar Kyoto rats, Amino Acids 2012 (2012).

[37] Z.M.a.A.-A. Abdallah, F.T. , Some biochemical studies of diazepam (valium) on rabbit brain homogenate, Arab J. Med, 8 (1982) 131-139.

[38] M. Schlumpf, W. Lichtensteiger, H. Langemann, P.G. Waser, F. Hefti, A fluorometric micromethod for the simultaneous determination of serotonin, noradrenaline and dopamine in milligram amounts of brain tissue, Biochemical pharmacology, 23 (1974) 2437-2446.

[39] J. Parratt, G. West, Release of 5- hydroxytryptamine and histamine from tissues of the rat, The Journal of physiology, 137 (1957) 179-192.

[40] M.M. Parker, F.L. Humoller, D.J. Mahler, Determination of copper and zinc in biological material, Clinical chemistry, 13 (1967) 40-48.

[41] N. Ozaki, D.M. Chuang, Lithium Increases Transcription Factor Binding to AP- 1 and Cyclic AMP- Responsive Element in Cultured Neurons and Rat Brain, Journal of neurochemistry, 69 (1997) 2336-2344.

[42] T. Baptista, L. Teneud, Q. Contreras, J. Burguera, M. Burguera, L. Hernandez, Effects of acute and chronic lithium treatment on amphetamine-induced dopamine increase in the nucleus accumbens and prefrontal cortex in rats as studied by microdialysis, Journal of Neural Transmission/General Section JNT, 94 (1993) 75-89.

[43] M. Dziedzicka-Wasylewska, M. Maćkowiak, K. Fijaτ, K. Wędzony, Adaptive changes in the rat dopaminergic transmission following repeated lithium administration, Journal of Neural Transmission, 103 (1996) 765-776.

[44] J.-M. Aubry, M. Schwald, E. Ballmann, F. Karege, Early effects of mood stabilizers on the Akt/GSK-3β signaling pathway and on cell survival and proliferation, Psychopharmacology, 205 (2009) 419-429.

[45] S. Nuutinen, P. Panula, Histamine in neurotransmission and brain diseases, in: Histamine in Inflammation, Springer, 2010, pp. 95-107.

[46] X. Yang, C. Liu, J. Zhang, H. Han, X. Wang, Z. Liu, Y. Xu, Association of histamine N-methyltransferase Thr105Ile polymorphism with Parkinson's disease and schizophrenia in Han Chinese: a case-control study, PloS one, 10 (2015) e0119692.

[47] M. Vizuete, M. Merino, J. Venero, M. Santiago, J. Cano, A. Machado, Histamine infusion induces a selective dopaminergic neuronal death along with an inflammatory reaction in rat substantia nigra, Journal of neurochemistry, 75 (2000) 540-552.

[48] P. Langlais, S. Zhang, G. Weilersbacher, L. Hough, K. Barke, Histamine- mediated neuronal death in a rat model of Wernicke's encephalopathy, Journal of neuroscience research, 38 (1994) 565-574.

[49] P. Nowak, A. Bortel, J. Dabrowska, I. Biedka, G. Slomian, W. Roczniak, R.M. Kostrzewa, R. Brus, Histamine H 3 receptor ligands modulate L-dopa-evoked behavioral responses and L-dopa-derived extracellular dopamine in dopamine-denervated rat striatum, Neurotoxicity research, 13 (2008) 231-240.

[50] L.H. Price, D.S. Charney, P.L. Delgado, G.R. Heninger, Lithium and serotonin function: implications for the serotonin hypothesis of depression, Psychopharmacology, 100 (1990) 3-12.

[51] N. Crespo-Biel, A. Camins, M. Pallas, A. Canudas, Evidence of calpain/cdk5 pathway inhibition by lithium in 3-nitropropionic acid toxicity in vivo and in vitro, Neuropharmacology, 56 (2009) 422-428.

[52] R. Bernasconi, The GABA hypothesis of affective illness: influence of clinically effective antimanic drugs on GABA turnover, in: Basic mechanisms in the action of lithium, Excerpta Medica Amsterdam, 1982, pp. 183-192.

[53] L. Ferrie, A.H. Young, R. McQuade, Effect of chronic lithium and withdrawal from chronic lithium on presynaptic dopamine function in the rat, J Psychopharmacol, 19 (2005) 229-234.

[54] J.R. Moffett, B. Ross, P. Arun, C.N. Madhavarao, A.M. Namboodiri, N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology, Prog Neurobiol, 81 (2007) 89-131.

[55] M. Yudkoff, Y. Daikhin, T.M. Melo, I. Nissim, U. Sonnewald, The ketogenic diet and brain metabolism of amino acids: relationship to the anticonvulsant effect, Annu Rev Nutr, 27 (2007) 415-430.

[56] G. Chen, P.X. Yuan, Y.M. Jiang, L.D. Huang, H.K. Manji, Lithium increases tyrosine hydroxylase levels both in vivo and in vitro, J Neurochem, 70 (1998) 1768-1771.

[57] M. Sparapani, M. Virgili, F. Ortali, A. Contestabile, Effects of chronic lithium treatment on ornithine decarboxylase induction and excitotoxic neuropathology in the rat, Brain Res, 765 (1997) 164-168.

[58] E. Severus, M.J. Taylor, C. Sauer, A. Pfennig, P. Ritter, M. Bauer, J.R. Geddes, Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis, Int J Bipolar Disord, 2 (2014) 15.

[59] J. Kasuya, G. Kaas, T. Kitamoto, Effects of lithium chloride on the gene expression profiles in Drosophila heads, Neurosci Res, 64 (2009) 413-420.

[60] C.T. Chiu, Z. Wang, J.G. Hunsberger, D.M. Chuang, Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder, Pharmacol Rev, 65 (2013) 105-142.

[61] T. Dudev, C. Lim, Competition between Li+ and Mg2+ in metalloproteins. Implications for lithium therapy, Journal of the American Chemical Society, 133 (2011) 9506-9515.

[62] H. Gonullu, E. Gonullu, S. Karadas, M. Arslan, O. Kalemci, A. Aycan, R. Sayin, H. Demir, The levels of trace elements and heavy metals in patients with acute migraine headache, J Pak Med Assoc, 65 (2015) 694-697.

[63] U. Gröber, J. Schmidt, K. Kisters, Magnesium in prevention and therapy, Nutrients, 7 (2015) 8199-8226.

[64] S. Gupta, A. Manhas, V. Gupta, R. Bhatt, Serum magnesium levels in idiopathic epilepsy, The Journal of the Association of Physicians of India, 42 (1994) 456-457.

[65] T. Yary, S.M. Lehto, T. Tolmunen, T.-P. Tuomainen, J. Kauhanen, S. Voutilainen, A. Ruusunen, Dietary magnesium intake and the incidence of depression: A 20-year follow-up study, Journal of affective disorders, 193 (2016) 94-98.

[66] A.K. Baltaci, F. Sunar, R. Mogulkoc, M. Acar, H. Toy, The effect of zinc deficiency and zinc supplementation on element levels in the bone tissue of ovariectomized rats: histopathologic changes, Archives of physiology and biochemistry, 120 (2014) 80-85.

[67] C.d.P. Eduardo, A. Simões, P.M. de Freitas, V.E. Arana- Chavez, J. Nicolau, V. Gentil, Dentin decalcification during lithium treatment: case report, Special Care in Dentistry, 33 (2013) 91-95.

[68] K. Szydlowska, M. Tymianski, Calcium, ischemia and excitotoxicity, Cell calcium, 47 (2010) 122-129.

[69] M.J. Berridge, C.P. Downes, M.R. Hanley, Neural and developmental actions of lithium: a unifying hypothesis, Cell, 59 (1989) 411-419.

[70] N. Sourial-Bassillious, P.-A. Rydelius, A. Aperia, O. Aizman, Glutamate-mediated calcium signaling: a potential target for lithium action, Neuroscience, 161 (2009) 1126-1134.

[71] C.-T. Chiu, D.-M. Chuang, Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders, Pharmacology & therapeutics, 128 (2010) 281-304.

[72] A. Harwood, Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited, in, Nature Publishing Group, 2005.

Figure legends:

Fig 1: The effect of therapeutic doses of lithium carbonate (75 mg/kg) on dopamine and magnesium contents of rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at $P < 0.05^{*}$).

Fig 2: The effect of therapeutic doses of lithium carbonate (75 mg/kg) on histamine and calcium contents in rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at $P < 0.05^{*}$).

Fig 3: The effect of therapeutic doses of lithium carbonate (75 mg/kg) on glycine, γ-aminobutyrate, histidine, phenylalanine and tyrosine contents in rat brain tissue extract after 2 hrs, 2 weeks and one month of oral administration (Values are expressed as mean ± SE and are considered significant than control group at $P < 0.05^{*}$).