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Bivalent Cations in Bipolar Disorders

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1. Introduction

Bivalent cations play a lot of roles in human brain. Calcium, magnesium zinc ,copper and other cations are involved in normal functions of the brain .The most important mechanisms of action for cations are : modulation of the presynaptic release of some neuromediators , influence on neuronal ionic channels, induction of changes in some receptors activity, influence on the transporters of neuromediators. The disbalance in intracellular or extra cellular concentrations of brain cations are observed in neurological and psychiatric diseases (major depression, schizophrenia, heroine addiction, neurodegenerative diseases, convulsive disorders). The bipolar disorder(BP) is a major public health problem. The economic cost is high and the patients have a high risk of suicide(Antelman et al. 1998) BD also called manic-depressive psychosis is a relative frecvent psychiatric ill. The pathogenic mechanism of the development of BD is unknown yet. The aetiopathogenesis of BD will be better elucidated in the future by experimental and clinical studies.

2. Bipolar cations in bipolar disorders

There are few data , sometimes contradictory regarding the variation of concentration of bivalent cations in the patients with BD. Herzberg & Herzberg 1977 observed a decreased level for plasma magnesium in BD patients compared to healthy control group. Carman et al. 1979 found an increased plasma ratio calcium/ magnesium in BP patients correlated to the intensity and duration of maniacal agitation. The plasma zinc levels were decreased in acute maniacal agitation. Contrary, Frazer et al. 1983 found a higher erythrocyte magnesium level in BD patients not correlated with the severity of clinical symptoms . George et al.1994 showed an increased level of cerebro-spinal fluid magnesium and lack of correlation with the clinical course of mood modulators therapy. Our data (Nechifor et al 2006,2007) show that adult patients with bipolar disorder type I presenting acute maniacal attacks and no previous treatment exhibit lower intracellular magnesium levels than control group. Plasmatic zinc concentrations was significantly lower . There were no significant differences between patients with bipolar disorder type I and control group regarding total magnesium plasma concentration.. An exaggerated intracellular calcium level and an exaggerated of cytosolic calcium concentration in response to serotonin are showed in depressive phase of BD and in major depression. Brown et al .2007 observed clinical maniacal symptoms in the

cases of hyperthyroidism in patients with hypercalcemia. The plasma zinc levels were decreased in acute maniacal agitation. The existence of many clinical forms of BD contributes to the heterogeneity of obtained data.

3. Our studies on bivalent cations level in patients with bipolar disorders

After DSM IV bipolar disorders are classified in four groups. In the bipolar disorder type I the patient has mixed maniac and depressive symptoms with at least one maniac episode. All the patients from our study have been the type I bipolar disorder patients. The mood modulators are the treatment of choice today for BD. Some anticonvulsant drugs are the main choice drugs today in BD treatment (Goodnick 2006, Muzina et al. 2005, Bowden et al. 2006). Carbamazepine and sodium valproate are usually used in BD therapy (Weisler et al. 2005, Walden et al. 1993). The aim of our research was the determination of the plasma and the intracellular levels of some bivalent cations in BD patients before the treatment and also the study of the influence of mood modulators influence on cations concentration during BD therapy. We determined the levels of plasma calcium, magnesium, copper and zinc and the erythrocyte magnesium concentration in adult patients with BD type I (after DSM IV). We worked on adult patients with bipolar disorders (BD) (diagnosed after DSM IV criteria) ageing 21-58 years. Admitted into "Socola Psychiatric Hospital" Iasi Romania. In the study were included only type I BD adult patients hospitalized during the maniacal episode. We worked on three groups of patients: I group received carbamazepine 600mg/day p.o. daily 4 weeks; II group received sodium valproate 900mg/day p.o. daily 4 weeks; III group received quetiapine 400-600mg/day p.o. daily 4 weeks. A group of 20 healthy adults was control group.

Including criteria: bipolar disorder (diagnosed after DSM IV), at least 4 weeks treatment, absence of any BD treatment before admittance in hospital. All patients did not received any treatment for BD before hospitalization. The following non-including criteria were used: pregnancy, lactation, renal failure, heart failure, hepatic failure, malabsorption syndrome, treatment with bivalent cations containing drugs or diuretics treatment. The plasma levels of total calcium, total magnesium, zinc and copper and erythrocyte magnesium level were determined by atomic absorption spectrophotometry. The determination was performed before the start of treatment and after 4 weeks. In this study were included only patients with at least 4 weeks hospitalization. The results were statistically interpreted.

3.1 Results

The obtained data showed that zinc plasma level was decreased in BD patients before treatment compared to control group. ($0.89 \pm 0.12 \text{ mg/l}$ in control group vs. $0.62 \pm 0.05 \text{ mg/l}$ in BD group $p < 0.05$). No changes in total calcium plasma concentration ($116.32 \pm 9.1 \text{ mg/l}$ in BD patients vs. $109.20 \pm 12.3 \text{ mg/l}$ in control group). The erythrocyte magnesium level was decreased in BD patients before treatment ($45.01 \pm 1.67 \text{ mg/l}$ in BD patients vs. $59.15 \pm 2.01 \text{ mg/l}$ in control group $p < 0.05$). The copper concentration was increased in BD patients before treatment compared to control group. After 4 weeks of treatment the plasma zinc concentration increased in all group of treated patients (ex. after sodium valproate, Zn concentration was $0.83 \pm 0.04 \text{ mg/l}$ $p < 0.05$). The erythrocyte magnesium level increased in all

treated patients (ex. in carbamazepine group after treatment Mg concentration was $53.72 \pm 2.18 \text{ mg/l}$ $p < 0.05$),but only in quetiapine treated group , the total plasma magnesium concentration significantly increased. In all treated groups copper plasma concentration decreased after the treatment Did non changes in calcium plasma levels after mood modulators treatment. Our results showed that zinc plasma concentration and erythrocyte magnesium level are decreased during the maniacal acute episode of type I BD patients . The obtained data showed that different mood modulator with different mechanism of action increased zinc plasma level and decreased copper plasma concentration. The erythrocyte magnesium is also increased. There are good positive correlations between the improvement of clinical status of patients and the increase of zinc plasma concentration and the augmentation of intracellular magnesium levels.

4. Interactions between mood modulator and bivalent cations

4.1 Magnesium

The mood modulators used in the treatment of BD induced important changes in some bivalent cations concentrations. The increase of magnesium intracellular concentrations were observed after all three mood modulators used. There are data showed that lithium , the oldest effective drug for the treatment of maniac-depressive illness increases the intracellular magnesium levels .Most studies show that the repeated lithium salts administration increases the magnesium concentration.

Lithium increases the intracellular magnesium concentration by competition between magnesium and lithium for some intracellular binding sites(Leyden et al.2000, Mota de Freitas et al.2006)After experimental loading of neuroblastoma cells with 1-2 mM of extracellular Li^+ , the intracellular free magnesium concentration was significantly higher . Regarding the Li^+ - Mg^{2+} competition at some intracellular sites , the existing data indicate the following targets :molecules:inositol monophosphatase, glycogen syntase kinase(GSK 3), fructose 1,6 biphosphatase, biphosphate nucleotidase , ADP and ATP phosphate bindind sites but it is possible to be also and other intracellular binding sites for this competition.(Gould et al. 2004)

The main ways for magnesium action in BD are :a)decreasing the neuronal response to glutamate overstimulation by blocking the calcium channel coupled with NMDA receptors;b) the decreasing presynaptic release of some excitatory neuroaminoacids; c) modulator action at the level of gabaminergic and serotoninerbic systems. Gobbi & Janiri ,2006 showed that magnesium-valproate significantly modulates the response induced by NMDA-receptor stimulation. Chuinard et al. 1990, showed that magnesium aspartate administration was effective in stabilizing the mood of rapid-cycling BD which favor the idea that the increase in magnesium concentration is an important factor of lithium and other mood modulators mechanism of action. Magnesium oxide increases the verapamil maintenance therapy in mania (Giannini et al 2000). This fact favors the idea that an increase in magnesium concentration is an important fact, maybe essential for the therapeutic effect of some drugs used in BD treatment. Magnesium-valproate reduces the hyperactivity in an animal model of mania. This effect of magnesium valproate could be abolished by bicuculine.These findings suggest that the action on the postsynaptic GABA effect may be involved also in magnesium-valproate antimaniacal action (Cao & Peng , 1993). The

neuroprotective magnesium effect in CNS is important not only for the recovery process after various injury (Vink & Cernak 2000) but also to reduce the maniacal agitation.

Machado-Viera R. et al. 2009 showed that the neurotrophic effect of lithium is very important for neuro protection (Rowe & Chuang 2004) and for prophylaxis of acute mood effects and one of the main targets of lithium intracellular action is GSK-3. By action at the level of this enzyme, Li increase the intracellular level of magnesium. It is possible that, at least in part, the reduction of apoptosis by lithium is produced by magnesium ions which inhibit the apoptosis. There are few studies about the magnesium alone effect in the treatment of bipolar disorders. Chouinard et al. 1990 showed a moderate effect of magnesium treatment as mood stabilizer for rapid cycling bipolar affective patients. Another way to explain the effect of magnesium and zinc in BP disorders is the antioxidant effect. The oxidative stress is increased in animal models of mania produced by amphetamine administration. Chronic amphetamine treatment is associated with an imbalance in SOD and CAT activity. In experimental studies in rats lithium and valproate prevented the excitotoxicity by reducing the oxidative stress (Shao et al. 2005). Both magnesium and zinc have an antioxidant effect. Another target for magnesium involvement in mood stabilizers therapeutic effect is BDNF (brain derived neurotrophic factor). The mood modulators (Frey et al. 2006) but also magnesium increase the BDNF concentration. The ratio between calcium and magnesium and the antagonist effect of magnesium regarding some calcium action are essential for explanation of importance of magnesium in mechanism of mood modulators effects. The transmembrane calcium influx plays an important role in the development of some psychiatric disorders. In BD has been observed dysfunctions in the intracellular signaling transduction, altered calcium signaling and an elevated protein kinase A activity (Langan & McDonald 2009).

The calcium channels antagonists (verapamil and others) raise carbamazepine effect. Magnesium, acting like a natural calcium antagonist on some ionic channels is a factor which contributes at the pharmacodynamic effect of some mood modulators. Contrary, the calcium ions have an antagonistic effect on carbamazepine action. Carbamazepine reduces the neuronal excitability and glutamate release and we consider that this effect is due at least in part by increasing the magnesium concentration. The alteration of calcium homeostasis is involved in the onset or progression of various neurological and psychiatric diseases such as Parkinson's disease, Alzheimer's and others degenerative diseases, bipolar disorders, Huntington's disease and others (Salvaraj et al. 2010). The hypercalcemia and the change of the ratio calcium/ magnesium could be involved in the pathophysiology of bipolar disorder. Maniacal clinical symptoms from hyperparathyroidism are mediated by hypercalcemia. The patients with maniacal symptoms had a high level of calcium in the blood and cerebrospinal fluid. The bipolar disorder is not the single disease in which are involved calcium signaling abnormalities in the central nervous system. Cytosolic Ca^{2+} signals are correlated to extracellular calcium enters through plasma membrane channels and to the calcium release from the intracellular stores. In some diseases as seizures, migraine and autism is possible to be genetic calcium signaling abnormalities (Gargus 2009).

The main mechanism of action of mood modulators in BD is the reduction of the glutamatergic systems activity via NMDA receptors activation. The key common point of magnesium and zinc action in BD is NMDA glutamate receptors. Magnesium ions and some calcium antagonists act also at the level of NMDA receptors coupled calcium channel

The changes in calcium homeostasis are important in the pathophysiology of the bipolar disorder. (Akimoto et al. 2007). Calcium enhance NMDA receptor activity and stimulate the presynaptic glutamate release. There are evidences of abnormalities in intracellular calcium distribution, concentration and activity and for the involvement of calcium homeostasis dysregulation in the molecular mechanism of this disease. Perova T. et al. 2007 showed a hyperactive intracellular calcium dynamics in the lymphoblasts from patients with type I bipolar disorder. Acting as a calcium antagonist, magnesium can reduce in part calcium effects in bipolar disorders. Yasuda et al. 2009 showed that for mood modulators as valproic acid and lithium, the GSK-3 inhibition and the stimulation of brain-derived neurotrophic factor (BDNF) synthesis are the primary targets in the action mechanism involved in the suppression of bipolar disorders symptoms. BDNF is strongly involved in the synaptic plasticity, reduces the apoptosis, increase the neuronal survival and regulates the expression of NMDA receptors in brain (Caldeira et al 2007). Magnesium is also involved in neuronal plasticity, inhibits the apoptosis and reduces the neurotoxicity of high glutamate concentration and of overstimulation of NMDA receptors. The kainate-induced neurotoxicity is produced after stimulation of NMDA receptors and lithium decreases this toxicity. Also the NMDA receptors mediated neuronal vacuolization is attenuated by mood modulators (Bown et al. 2003). Crespo-Biel et al. 2010 showed that this neuroprotective effect is produced by modulation of calcium entry in neurons. By reducing the calcium penetration in the cell, magnesium can be involved in the neuroprotective lithium effect. The mood modulators have also an important antiapoptotic action (Chuang et al. 2005). Magnesium has a important antiapoptotic action and can be involved in this action of mood modulators. We believe that the increase of intracellular magnesium concentration is also a primary step in mood modulators mechanism of action. Bipolar disorder patients have a high rate of relapse (Newberg et al. 2008). The Ca^{2+} -permeable melastin related transient receptor potential 2 (TRPM2) channels are important for the entry of calcium ions into the cell. The genetic variations of TRPM 2 increases the risk of developing bipolar disorders (Naziroglu 2011). There are data implicating L-type calcium channels dysfunctions in the pathophysiology of neuro psychiatric disorders (Casamassima et al. 2010). In mood disorders, L-type calcium channels blockers reduced in clinical practice the intensity of clinical symptoms. In the animal models of depression the calcium channels blockers had a similar effect. Glutamate stimulates NMDA receptors and increases the entry of calcium in neurons. Verapamil, a calcium channels antagonist augmented the lithium effects in the treatment of mania. In some studies, verapamil alone has shown antimanic effect. (Mallinger et al. 2008), but the verapamil monotherapy has a reduced efficacy in BD type I patients. In the experimental model of depression induced by forced swim test in rats and in the tail suspension test in mice, zinc administration exerts an antidepressant effect (Krocicka et al. 2001, Rosa et al. 2003). Magnesium oxide increases the verapamil maintenance therapy in mania (Giannini et al 2000). This fact favors the idea that an increase in magnesium concentration is an important fact, maybe essential for the therapeutic effect of some drugs used in BD treatment. Magnesium-valproate reduces the hyperactivity in an animal model of mania. This effect of magnesium valproate could be abolished by bicuculline. These findings suggest that the action on the postsynaptic GABA effect may be involved also in magnesium-valproate antimanic action (Cao & Peng, 1993).

Lithium improves the cognitive deficits in animal models of neurodegenerative diseases. Magnesium also increases the memory in experimental studies. It is possible that, in part, the cognitive effect of lithium be intermediated by the increase of magnesium intracellular concentration.

Magnesium potentiates the effects of anxiolytics. There are experimental evidences of the potentiation of anxiolytic effect of diazepam by magnesium aspartate (Borzeix et al. 1991).

To the extent that glutamatergic signaling *via* NMDA receptors is pathologically upregulated in bipolar disorder patients, (Toro & Deakin 2005, Hashimoto et al. 2007) The modulation of signal transduction at the level of glutamate, serotonin, dopamine and GABA receptor by the mood modulators has major therapeutic involvements (Manji et al. 1999) Valproic acid interferes with glutamatergic function and NMDA receptor signaling., Valproic acid acts at the level of NMDA receptors by different ways (Gean et al. 1994). This drug reduces induction of Fos and of activator protein-1 DNA binding activity. By this mean is modulated the transcription of the NMDA receptor subunit, NR2B. Chronic valproate treatment blocks D(2)- receptor-mediated brain signaling via arachidonic acid in rats. By inhibiting NMDA receptors mediated calcium influx, lithium and magnesium suppresses the calcium dependent way for activation of apoptotic signaling pathways (Chiu & Chuang 2011) Lamotrigine is another mood modulator used in bipolar disorder which has a key point of mechanism of action the blocking effect of NMDA receptor mediated signaling in the brain (Ramadan et al 2011).

Substances that interfere with dopaminergic (Murphy et al. 1971) or glutamatergic (Anand et al. 2000) signaling ameliorate bipolar disorder symptoms. Bipolar symptoms reflect reduced cholinergic (Bymaster et al. 2002), altered serotonergic, and increased dopaminergic and glutamatergic neurotransmission. The mood-stabilization of bipolar patients appear only after 10 days or more time administration. We think that the retardation of effect appears because needs time for increasing the intracellular magnesium concentration. Our data showed a good positive correlation between therapeutic effect and the increase the intracellular but not with the extracellular magnesium concentration. The acute administration of a single dose of mood modulators don't change the glutamate level but also don't modify the magnesium concentration. The therapeutic effect of carbamazepine in the treatment of epilepsies and in affective disorders was decreased by a low magnesium level in patients effect (Walden et al. 1993). Another possibility for magnesium beneficial effect in the treatment of BD by various mood modulators is action at the level of GABA-ergic systems from the CNS. Magnesium valproate decreased the hypermotility in experimental rodent model of mania but this effect is diminished by bicuculline, substance which blocks GABA receptors. (Cao & Peng 1993) This fact involves the post synaptic GABA receptors in magnesium effect in BD. Magnesium can modulate the GABA receptors activity and there are evidence for a potentiating effect of magnesium at the level of GABA A receptors (Moykkynen et al. 2001). The interactions between magnesium and lithium are very complex because there are possibilities that magnesium increase the lithium entry into the cells. (Rybakowski & Szajnerman 1976).

4.2 Copper

The increase of copper level could be also involved in the pathogenesis of bipolar disorders. Mood disorders are frequently reported in Wilson disease. Manic symptoms and depressive behavior are present in patients with high level of copper. (Keller et al. 1999, Akil & Brewer 1995). In 20% of patients, the psychiatric manifestations preceded all other symptoms. (Dening & Barrios 1989, Machado et al. 2008). The mechanism of action of increased copper concentration in mood disorders is not clear but we believe that the influence on dopamine neuromodulation and the possible increase of glutamatergic system activity is important. Studies performed in rats showed that copper has an opposite effect on the compared to magnesium and zinc. Copper-dopamine complex induced mitochondrial autophagy and the neuronal death (Paris et al. 2009). In the same time, the stimulation of synaptic NMDA receptors by glutamate in hippocampus neurons is associated to the release of copper from intracellular stocks. A copper efflux after NMDA receptors activation was observed. Unlike magnesium and zinc, copper could function as a metal involved in nitrosylation of NMDA receptors. Surely, copper is a neuromodulator factor of some brain area as hippocampus.

GABA is one of the factors involved in the reduction in intensity of opiate dependence, as well as in the reduction in intensity of opiate-withdrawal syndrome signs. At least in some brain areas, copper blocks GABA receptors. Copper and zinc interact at the level of GABA receptors (Sharonova et al. 2000). The copper-GABA complex antagonized diazepam anticonvulsant effect (Kardas et al. 1984). This shows that by forming a complex with GABA, copper ions reduce the efficacy of this amino-acid in antagonizing glutamate effects during the development of morphine dependence.

4.3 Zinc

Zinc allosterically modulates the 5-HT (1A) serotonin receptors (Barrondo & Salles 2009). By this way, zinc can be an important factor influencing the antidepressant and mood modulators therapy. This cation modulates also the neurotransmitters activity including dopamine and serotonin transporters. (Norgaard-Nilsen & Gether 2006). Regarding main ways by which the increase of zinc concentration can be involved in the mechanism of mood modulators action, very important is zinc effect on the NMDA receptors. By stimulation of NMDA receptors, glutamate induces agitation and anxiety. Zn^{2+} decreases the NMDA receptor stimulation. Increased zinc concentration in amygdala decreases the fear and the anxiety (Takeda et al. 2010). The antidepressant action involved also the serotonergic system (Szewczyk et al. 2009, Garcia-Colunga et al. 2005). Serotonin is a big target for antidepressant drugs (Harvey 1997). An important number of very used antidepressant drugs are substances which block serotonin re-uptake. The chronic lithium treatment influences the cortical serotonin uptake and 5-HT_{1A} receptors activity (Carli et al. 1997). Zinc modulates the lithium induced biochemical and behavioral changes in rats (Bhalla et al. 2007).

Zinc modulates the serotonin uptake in some areas from the brain. The effects of fluoxetine, imipramine and 6-nitroquipazine on serotonin uptake in rat brain are modulated by zinc (Garcia-Colunga et al. 2005). Serotonin induced platelet calcium mobilization is enhanced in BD patients (Okamoto et al. 1995, Akimoto et al. 2007). In the experimental model of depression induced by forced swim test in rats and in the tail suspension test in mice, zinc

administration exerts an antidepressant effect (Krocicka et al. 2001, Rosa et al. 2003, Opoka et al. 2009) . There are experimental data about a complex zinc-induced adaptive and modulatory changes in glutamateric and serotonergic brain systems(Cichy et al. 2009).In our clinical studies (Nechifor et al. 2004, Nechifor 2008) the plasma zinc concentration was decreased and the antidepressant treatment augmented the level of this cation. Chronic lithium administration reduced the NMDA receptors signaling also via arachidonic acid and eicosanoids synthesis(Basselin et al. 2006)but is not clear if zinc or magnesium influence this way.

4.4 Calcium

Calcium ions play a very important role in biological signal transduction, in synthesis and release of neuromediators and neuromodulators and in the several enzymes activity. The calcium neuronal activity in bipolar disorders is increased. There are studies which showed that a elevation of basal calcium intracellular concentration in B D patients (Emamghoreishi et al .1997, Du et al. 2004) .

A way for the involvement of calcium in bipolar disorders pathogeny is PKC activity. This enzyme potentiates the the response after NMDA receptors stimulation by increasing the calcium entry by the channel coupled with NMDA receptors and by reducing the voltage – dependent magnesium block of this channel (Chen & Huang 1992)PKC also up-regulates the function of L-type calcium channels and the entry of calcium into the cell(McCarty 2006). Magnesium can decrease this mechanism involved in BD. Valproate, lithium and other mood modulators decrease also the PKC activity(Mallinger et al.2008) .The increase of intracellular magnesium concentration can be a common point for the antimanic and antidepressive action.

5. Conclusions

The increase of intracellular magnesium concentration by different mood modulators which various chemical structures and different mechanism of action shows that this is important for the therapeutic effect in BD treatment. On the other hand, this magnesium intracellular concentration change is associated with an significant augmentation of plasma zinc level and decrease of plasma copper concentration We consider that there changes is in important part of the mechanism of pharmacotherapeutic action of mood modulators. We believe that the bivalent cations disbalances are involved in the B D relapses and also in the reduction of efficacy of the mood modulators therapy.

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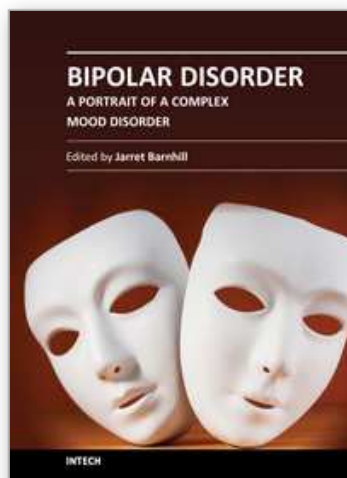
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Bipolar Disorder: Portrait of a Complex Mood Disorder is a step towards integrating many diverse perspectives on BD. As we shall see, such diversity makes it difficult to clearly define the boundaries of BD. It is helpful to view BD from this perspective, as a final common pathway arises from multiple frames of reference. The integration of epigenetics, molecular pharmacology, and neurophysiology is essential. One solution involves using this diverse data to search for endophenotypes to aid researchers, even though most clinicians prefer broader groupings of symptoms and clinical variables. Our challenge is to consolidate this new information with existing clinical practice in a usable fashion. This need for convergent thinkers who can integrate the findings in this book remains a critical need. This book is a small step in that direction and hopefully guides researchers and clinicians towards a new synthesis of basic neurosciences and clinical psychiatry

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