Review

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Lithium – therapeutic tool endowed with multiple beneficiary effects caused by multiple mechanisms

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Mood disorders are relatively common serious human diseases for which there is often no ideal pharmacotherapy. Basic characteristic of these diseases is affective disorder shifting the mood of the patient to depression (together with anxiety or not) or towards to euphoria. Available drugs are usually divided into two groups – mood stabilizers, which are used primarily to treat bipolar disorder, and antidepressants for the treatment of unipolar depression. Lithium is still recommended as the first choice for dealing with bipolar disorder. Despite abundant clinical use of mood stabilizing drugs, important questions regarding their mechanism of action remain open. In this paper we present the brief review of rather diversified hypotheses and ideas about mechanisms of genesis of mood disorders and lithium interferences with these pathological states. New data derived from the high-resolution crystallographic studies of allosteric, Na^+-binding sites present in G protein coupled receptors are given together with data indicating the similarity between lithium and magnesium cations. In this context, similarities and dissimilarities between the useful "poison" with narrow therapeutic window (Li^+) and the bivalent cation acting like cofactor of more than 300 enzymatic reactions (Mg^{2+}) are pointed out together with results indicating enhanced activity of trimeric G proteins in bipolar disorder.

Key words: bipolar disorder, lithium, sodium, magnesium, G protein coupled receptors, Na^+-allosteric site.

INTRODUCTION

Mood disorders (affective disorders), including bipolar disorder and (unipolar) depression, are relatively common serious human diseases for which there is often no ideal pharmacotherapy. These diseases hold profound implications not only for the patients but also for their family members and the whole society. Basic characteristic of these types of diseases is affective disorder shifting the mood of the patient to depression (together with anxiety or not) or towards to euphoria. There are several treatment options for mood disorders. Available drugs are usually divided into two groups – mood stabilizers, which are used primarily to treat bipolar disorder, and antidepressants for the treatment of unipolar depression (Schloesser et al. 2012). Despite abundant clinical use of mood stabilizing drugs, important questions regarding their mechanism of action remain open.

Mood disorders are often difficult to diagnose. More than half of patients who turn to their general practitioners for depressive disorders are wrongly diagnosed (Avissar and Schreiber 2002). There is a huge gap between progress in the pharmacotherapy of these diseases and the current lack of objective biological tests for diagnosis (Avissar and Schreiber 2002). High risk of committing suicide in patients with mood disorders is a reason for finding clinically applicable methods for measuring biochemical changes that accompany these disorders. Such a method could facilitate the implementation of appropriate interventions.

Bipolar disorder is an episodic mood disorder characterized by two or more phases, during which mood and activity level of a patient are significantly disrupted. Under certain circumstances the bipolar patient is in elated or irritable mood or both and has increased activity (mania or hypomania – symptoms are less severe or less protracted than are those of mania), another time the patient is in low mood and has related symptoms such as loss of pleasure and reduced activity (depression). So, during this disease occur recurrent mood swings.

Bipolar disorder is a serious mood disease with a worldwide prevalence of 1–5% of the population (Avissar and Schreiber 2002, Schloesser et al. 2012, Amihaesei 2014, Can et al. 2014) and is an example of a psychiatric disorder that is very difficult to accurately diagnose (Singh and Rajput 2006, Phillips and Kupfer 2013). Genetic predisposition is one of the highest among psychiatric disorders. Heritability index is 0.85 (McGuffin et al. 2003). The risk of suicide is between 6% and 10%, i.e. 10 times

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higher than in the general population (Cipriani et al. 2013) and at about 10–20% of bipolar disorder patients commit suicide in the course of this disease (Rihmer and Kiss 2002, Gonzalez-Maeso and Meana 2006, Rybakowski 2013). Adequate treatment should allow the long-term remission and good functioning in majority of patients (Rybakowski 2013), however, the evidence regarding the efficacy of standard medical procedures, especially antidepressants, remain limited and inconsistent (Vazquez et al. 2013).

Mood stabilizers play the most important role in the long-term treatment of bipolar disorder. If some drug stabilizes mood symptoms associated with bipolar disorder, without affecting the others, the substance can be considered as a mood stabilizer (Baldessarini 2013). Mood stabilizer should ideally be effective in treatment of both poles (manic and depressive) of the acute symptoms of bipolar disorder equally and also prevent these symptoms (Bauer and Mitchner 2004). Current mood stabilizers, however, have mostly efficiency at one pole and lower efficiency on the other (Rybakowski 2013). Mood stabilizers used for treatment of bipolar disorder include lithium, anticonvulsants (valproate, carbamazepine, lamotrigine), antipsychotics (e.g. chlorpromazine, olanzapine, quetiapine etc.), and antidepressants (e.g. imipramine, iproniazid, meprobamate etc.) (Baldessarini 2013). Among mood stabilizers, lithium is regarded as unique therapeutic agent and the only true mood stabilizer in the management of bipolar disorder. It has held the pole position for more than half a century and is especially effective in treating acute mania and providing long-term prophylaxis. Its profound anti-suicidal properties further justify its use in bipolar disorder (Malhi et al. 2013).

LITHIUM

While the first discovery of therapeutic potential of lithium in bipolar disorder treatment in the late 40s of the 20th century is generally attributed to an Australian psychiatrist John Cade, it should be recognized that a number of considerations on the use of lithium salts in psychiatric conditions preceded his findings (Mitchell and Hadzi-Pavlovic 2000, Can et al. 2014, Oruch et al. 2014). It had been assumed, that many diseases, including psychological diseases, are the results of an imbalance of uric acid. In the 19th century lithium salts were used in the treatment of gout for their ability to dissolve uric acid crystals *in vitro* and later Lange and Hammond used independently lithium to treat mania (Mitchell and Hadzi-Pavlovic 2000, Baldessarini 2013, Can et al. 2014, Oruch et al. 2014). The final acceptation of lithium as an active substance for the treatment of bipolar disorder was significantly contributed by research of the Danish psychiatrist Mogens Schou and his colleague Poul Christian Baastrup (Schou et al. 1954, Baastrup and Schou 1967, Baastrup et al. 1970, Schou 1999).

Even though there is a decline in the use of lithium in the last few years, it is still recommended as the first choice for dealing with bipolar disorder according to all of the current medical handbooks (Grandjean and Aubry 2009b). Lithium is a typical mood stabilizer and has in this group of drugs a unique position. It has both the antimanic and extraordinary antidepressant activity; the antimanic effect being more pronounced than antidepressant. Unlike mood stabilizers that were originally indicated in the treatment of other diseases (anticonvulsants for treating epilepsy and antidepressants to treat schizophrenia), lithium is almost entirely effective in the treatment of mood disorders (Can et al. 2014). Moreover, there is evidence that lithium reduces the high risk of suicide in patients with bipolar disorder (Grandjean and Aubry 2009b, Kovacsics et al. 2009, Manchia et al. 2013). Only a subset of patients, however, shows therapeutic response to lithium (Can et al. 2014). Individual response to lithium is variable and has been reported as a heritable trait (Hou et al. 2016).

Clinical studies have also shown that lithium causes granulocytosis and lymphopenia while it enhances immunological activities of monocytes and lymphocytes. Lithium was used to treat granulocytopenia resulting from radiation and chemotherapy, to boost immunoglobulins after vaccination, and to enhance natural killer activity (Young 2009). Lithium acts through multiple pathways to inhibit glycogen synthase kinase 3β (GSK-3β). This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/β-catenin (WNT – wingless-type mouse mammary tumor virus integration site family). In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin-3 (NT3), as well as receptors to these growth factors in brain. Lithium also stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum and forebrain. The stimulation of endogenous neural stem cells may explain why lithium increases brain cell density and volume in patients with bipolar disorder. Lithium also increases brain concentrations of the neuronal markers *n*-acetyl-aspartate and myo-inositol. Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins. Lithium has been also reported to be beneficial in animal models of brain injury, stroke, Alzheimer's, Huntington's, and Parkinson's diseases, amyotrophic lateral sclerosis (ALS), spinal cord injury, and other conditions (Young 2009).

At neuronal level, lithium reduces excitatory (dopamine and glutamate) but increases inhibitory (GABA – γ-aminobutyric acid) neurotransmission; however, these broad effects are underpinned by complex neurotransmitter systems that strive to achieve homeostasis by way of compensatory changes. For example, at an intracellular

and molecular level, lithium targets second-messenger systems that further modulate neurotransmission. For instance, the effects of lithium on the adenylyl cyclase and phosphoinositide pathways, as well as protein kinase C, may serve to dampen excessive excitatory neurotransmission. In addition to these many putative mechanisms, it has also been proposed that the neuroprotective effects of lithium are keys to its therapeutic actions. In this regard, lithium has been shown to reduce the oxidative stress that occurs with multiple episodes of mania and depression. Further, it increases protective proteins such as brain-derived neurotrophic factor and B-cell lymphoma 2, and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 and autophagy. Overall, it is clear that the processes which underpin the therapeutic actions of lithium are sophisticated and most likely interrelated (Malhi et al. 2013).

Lithium transport across cell membrane

Lithium can be transported across the plasma (cell) membrane in several different ways (Reiser and Duhm 1982). The entry of lithium into the cell proceeds mainly as passive transport via voltage-gated sodium channels (Na^+_v). The Na^+-Li^+ counter-transport displaces lithium back from the cell interior to the extracellular space. In cells with physiological concentrations of Na^+ and K^+, the ouabain-dependent Na^+/K^+ pump mediates intake of Li^+, but is unable to release Li^+ back into extracellular space. Consequently, the intracellular concentration of lithium is increased in conditions of hyper-excitation of neuronal membrane (el-Mallakh and Wyatt 1995).

Li^+ enters the cells primarily through Na^+_v, because permeability of these channels for both cations is roughly equal (el-Mallakh 2004). Influx of Li^+ in this way is stimulated by veratridine and scorpion toxin; stimulation is blocked by tetrodotoxin. The pore diameter of Na^+_v is sufficiently limited, so that the small ions such as Na^+ and Li^+ can pass through the channel easily, but the transport of larger ions such as K^+ ions is significantly impeded. This allows Li^+ pass quickly through Na^+_v during neurotransmission. Consequently, the exogenously added Li^+ can spread rapidly throughout the body and enter neurons as well as skeletal and smooth muscle cells. It should be mentioned in this respect that ionic radius of non-hydrated lithium (0.68 Å) is smaller than of sodium (0.95 Å) and very close to the size of non-hydrated magnesium (0.65 Å) (Komoroski and Pearce 2008). It is therefore possible that the range of Li^+ effects proceeding in the cell interior and plasma membrane is based on competition with sodium and magnesium ions bound to variety of enzymes, transport and regulatory protein molecules. In this way, the overall cell metabolism (Young 2009) and synthesis and release of neurotransmitters across the plasma membrane may be altered (Komoroski and Pearce 2008).

The lithium efflux occurs mainly through an electrically neutral pump called Na^+-Li^+ counter-transporter (el-Mallakh 2004), which *in vivo* exchanges sodium for sodium, but also accepts lithium (Vaccaro et al. 2005). Lithium ions may replace sodium ions in this system and be transported via this carrier across the cell membrane in both directions (Mallinger et al. 1997). This transport route is not sensitive to ouabain or external K^+, is active in cell membranes of various types of tissues (Mallinger et al. 1997) and plays an important role in the biological disposition of clinically dosed lithium salts as during the lithium treatment, the Na^+-Na^+ exchanger is inhibited and the rate of lithium efflux decreased (Mallinger et al. 1997, Koltsova et al. 2011). The out-ward oriented movement of ions through Na^+-Li^+ counter-transport is (in the course of lithium-based therapy) decreased because of the reduced affinity of intracellular binding sites of this transporter for Li^+ (Mallinger et al. 1997). Therefore, the regulation of the speed of clearance of lithium from the cell contributes significantly to the therapeutic effects of lithium in the course of treatment of variety of psychiatric disorders (Mallinger et al. 1997, Koltsova et al. 2011).

Although the pathogenesis of bipolar illness is not yet fully understood, the several clearly defined pathophysiological abnormalities arising in acute, manic phase of the disease were described. One of the oldest and most consistent findings is the modified ion homeostasis: bipolar patients have increased intracellular sodium concentration, increased free intracellular calcium level and reduced activity of sodium plus potassium activated, ouabain-dependent adenosinetriphosphatase, Na^+/K^+-ATPase, in manic phase of bipolar disease (el-Mallakh and Wyatt 1995, el-Mallakh 2004). In manic phase of bipolar disease (mania) lithium ions enter the neurons in amounts exceeding capacity of its efflux and were found to be preferentially accumulated within the dendritic spines (el-Mallakh 2004). The benefaction by lithium was interpreted as extrusion of intracellular sodium thereby reducing (normalizing) intracellular sodium concentration ($[Na^+]_i$) and renewing the sodium electrochemical gradient across plasma membrane and resting membrane potential (el-Mallakh 2004).

Lithium affects a number of biochemical processes by competing with endogenous cations and, because most of these processes occur inside the cell, it is often said that the lithium mediates its therapeutic effects in the intracellular space of the brain neurons (Komoroski and Pearce 2008, Komoroski et al. 2013). Intracellular concentration of lithium is significantly lower than its concentration in the blood or extracellular fluid. This finding is important for models which have been proposed for its mechanism of action, since such a models must be able to explain

the effects of lithium at its intracellular concentration. However, in some *in vivo* cellular systems the very low intracellular concentrations of lithium were found (<10% of the extracellular) together with highly limited access of lithium to the intracellular space. Therefore, it has been also suggested that the mechanism of action of lithium may be partly based on interaction with external surface of plasma membrane (Birch 1994, Thellier et al. 1997).

Mechanism of lithium action in brain

The chemically simple substances such as lithium salts, which have a very important position in the treatment of bipolar disorder, do not have some clearly defined biological function in the body (Aral and Vecchio-Sadus 2008). Despite the abundant clinical use of lithium, the molecular mechanism of action by which this small monovalent ion exerts its therapeutic effects, remains still not elucidated. However, among many different effects of lithium salts which have been reported in the up to date literature (Odagaki et al. 1997, Minadeo et al. 2001, Srinivasan et al. 2004, Gonzalez-Maeso and Meana 2006, Gershon et al. 2009, Freland and Beaulieu 2012, Malhi et al. 2013, Keltner and Steele 2015), some represent the well-grounded theoretical basis for explanation of therapeutically significant reactions proceeding under *in vivo* conditions. All the mechanisms of lithium action discussed in this review are introduced in Fig. 1.

The major models for bipolar disorders were originally divided into two main categories: dendritic or postsynaptic models that focused on the function of trimeric G proteins and the secondary messengers such as Ca^{2+} and IP_3 (1,3,5-innositol trisphosphate); the axonal or presynaptic models that focused on membrane pumps and ion fluxes. The "sodium pump" hypothesis proposed that the decrease of activity of Na^+/K^+-ATPase may produce both mania and bipolar depression (el-Mallakh and Wyatt 1995). After 30 years of research and collection of experimental data from more clearly defined groups of bipolar patients which were distinguished from those suffering from other psychiatric disorders, the more refined hypotheses were formulated: lithium replaces sodium and alters intracellular calcium concentration; lithium inhibits the release and facilitates the uptake of primary messengers noradrenaline, serotonin and dopamine; lithium regulates Na^+/K^+-ATPase pump; lithium stabilizes the system of secondary messengers and regulates cAMP- and Ca^{2+}-dependent intracellular signaling cascades (Keltner and Steele 2015).

There are no doubts that abnormal mood states observed in bipolar disorder are associated with an increase in the concentration of intracellular sodium and calcium. It is therefore assumed that these changes may be causatively linked to the pathogenesis of this disease (el-Mallakh 2004). Particularly acute manic patients have increased sodium retention, increased overall body and intracellular sodium concentrations, increased intracellular free calcium concentration and reduced activity of Na^+/K^+-ATPase (el-Mallakh and Wyatt 1995). Curiously, reduction of Na^+/K^+-ATPase pump activity may be responsible for both phases of disease – mania and depression. Mania would be associated with an increase of $[Ca^{2+}]_i$ in pre-synaptic compartment, increased fusion of neurotransmitter containing vesicles with plasma membrane and increased stimulation of postsynaptic membrane (Ullrich et al. 1980, 1982, el-Mallakh 1983a, el-Mallakh and Wyatt 1995).

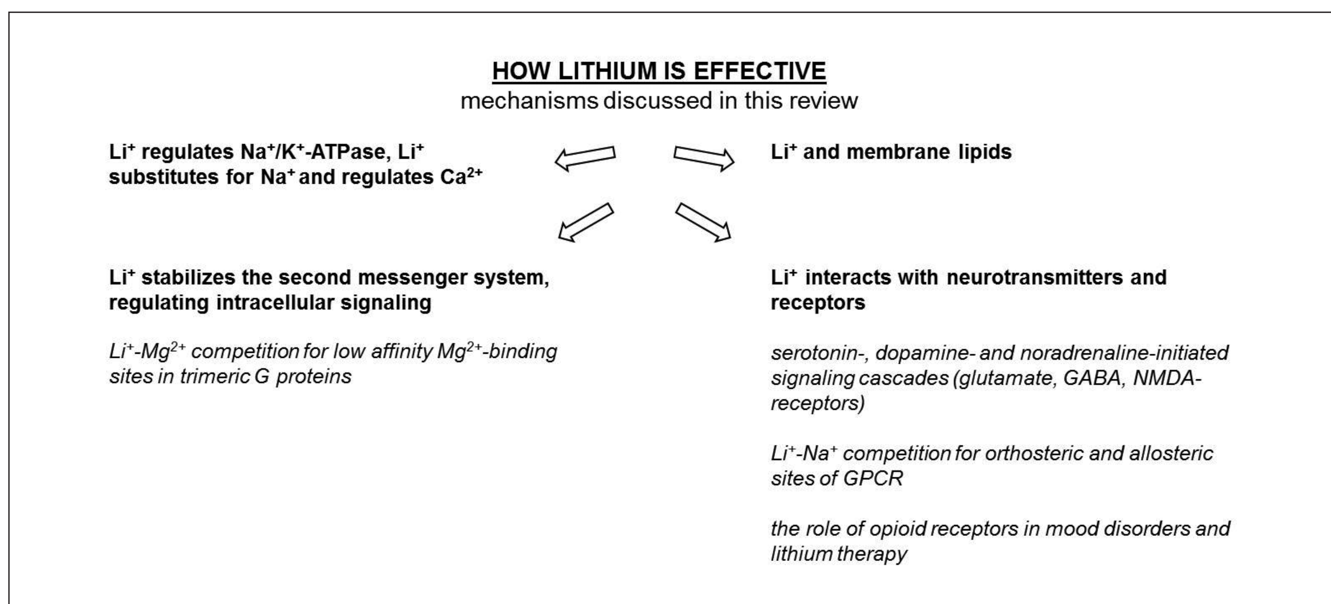

Fig. 1. Mechanisms of lithium action discussed in this review.

Depression would be consequently caused, when Na^+/K^+-ATPase activity is still decreased, by increased intracellular concentration of calcium, hydrolysis of PIP_2 and increased production of IP_3. In this way, the post-synaptic depolarization would proceed even in the absence of first messengers and lithium was suggested to be able to block this false, agonist-independent signaling (el-Mallakh and Li 1993). In support of this hypothesis, lithium was found to accumulate mainly in active neurons (el-Mallakh 1983b). As mentioned above, intracellular accumulation of lithium results in replacement of sodium, which in turn lowers $[Ca^{2+}]_i$. Decreased $[Ca^{2+}]_i$ normalizes the activity of neurons in both mania and depression.

When screening the other literature data, it may be generally said that lithium competes with sodium, potassium, calcium and magnesium in the nerve tissue. Impulse conduction is primarily altered by lithium ions attached to a range of different types of "binding sites" present in CNS. As the Li^+ ion radius is similar to the ionic radius of magnesium ions, Li^+ has the ability to compete with Mg^{2+}, which is a cofactor of wide variety of magnesium-dependent enzymes regulating the cell metabolism (Can et al. 2014). At therapeutic concentrations, lithium inhibits intracellular enzymes regulating secondary messenger levels: cAMP-dependent phosphodiesterases, inositol bisphosphate nucleotidases and inositol monophosphatases (Freland and Beaulieu 2012, Can et al. 2014).

Pharmacological research of affective disorders was also oriented to GPCRs (G protein coupled receptors) and, subsequently, to other membrane proteins regulating both the initial and following steps of GPCR-initiated signaling cascades. This area of research was most recently and thoroughly reviewed by Can and others (2014). Administration of lithium to rats (0.2% in food for 10 days) was found to inhibit specific [^{3}H]5-hydroxytryptamine (5-HT) binding and degree of inhibition of forskoline-stimulated adenylyl cyclase by 5-HT in hippocampal membranes. It also reduced [^{3}H]ketanserine binding and 5-HT-stimulated IP_3 production (Newman et al. 1990).

Alterations associated with depressive disorders of α2A-adrenergic (Callado et al. 1998, Gonzalez-Maeso et al. 2002, Sequeira et al. 2004), 5-HT1A serotonin (Sargent et al. 2000, Arango et al. 2001, Hsiung et al. 2003, Bhagwagar et al. 2004), μ-opioid (Gabilondo et al. 1995, Gross-Isseroff et al. 1998, Escriba et al. 2004) and CB1 cannabinoid (Hungund et al. 2004) receptors, both in terms of density and their functionality, were thoroughly tested and documented in numerous reports.

Mechanisms involving the interference of lithium with GPCR-G protein coupling were also analyzed rather early and the efforts to delineate the role of GPCR and G proteins in genesis and pharmacological treatment of bipolar disease continue since the present time (Avissar and Schreiber 2002). In 1988 it was first reported that trimeric G proteins are involved in basic biochemical mechanism of therapeutic action of lithium (Avissar et al. 1988, Avissar and Schreiber 2002). Lithium at therapeutically efficacious concentrations completely blocked both adrenergic and cholinergic stimulation of high-affinity binding of non-hydrolysable analog of GTP ([^{35}S]GTPγS – guanosine-5'-O-[γ-^{35}S]-triphosphate) to membranes prepared from rat cerebral cortex under both *in vitro* and *ex vivo* conditions. The same lithium treatment abolished guanine-nucleotides modulation of agonist binding (Avissar et al. 1988).

The coupling of both muscarinic-cholinergic receptors and β-adrenergic receptors to pertussis toxin-sensitive G proteins or cholera toxin-sensitive G proteins was compared in mononuclear leukocyte (MNL) membrane preparations isolated from untreated manic patients, lithium-treated euthymic bipolar patients and healthy volunteers (Schreiber et al. 1991). Hyperactive function of G proteins was detected in untreated manic patients. Both isoproterenol-induced and carbamylcholine-induced increases in Gpp(NH)p (5'-guanylyl imidodiphosphate) binding capacity were two-fold to three-fold higher than the increases observed in healthy volunteers. On the other hand, lithium-treated euthymic bipolar patients showed G protein responses to agonist activation that were no different from the healthy volunteers. An altered G protein function was therefore considered to have pathophysiological importance in genesis of bipolar disorder. Hyper-function of G proteins, changes in activity of PKC and PKA (protein kinase C and A) and cellular phosphorylation state in CNS were suggested to create an unstable "catastrophic" dynamic (oscillatory) system characteristic of a manic or depressive state. Lithium treatment attenuates G protein function and damps the oscillatory system to yield a stable state (Schreiber et al. 1991).

Lithium and glutamate signaling cascades

The serotonin-, dopamine- and noradrenaline-initiated signaling cascades have received the greatest attention in neurobiological studies of mood disorders as the majority of antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or noradrenaline (Can et al. 2014). However, the meaningful improvement of severe depressive symptoms (major depressive disorder and bipolar disorder) emerges only after several weeks of antidepressant therapy, suggesting that downstream neural adaptations rather than the elevation in synaptic monoamine levels itself are responsible for their therapeutic effects (Drevets 2001, Dunlop and Nemeroff 2007, Sanacora et al. 2008).

The search for the primary cause of mood disorders was therefore also oriented to analysis of mechanism of action of the major mediator of excitatory synaptic transmission in mammalian brain – glutamate (Orrego and Villanueva

1993). Under normal conditions, glutamate has a prominent role in synaptic plasticity, learning and memory, but under pathophysiological conditions it is known to be the powerful neuronal excitotoxin. In patients with bipolar disorder, glutamate concentrations were significantly increased in anterior cingulate cortex (ACC) and decreased in hippocampus (Ehrlich et al. 2015).

Patients with bipolar disorder are generally treated with a class of medicines known as mood stabilizers. Mood stabilizers have antimanic effects, exert prophylactic effects in preventing recurrent manic or depressive episodes and also exhibit antidepressant properties. The prototypical agent of this class of therapeutics is lithium. In view of the evidence that excessive synaptic glutamate may contribute to neuronal atrophy and degradation, it is noteworthy that chronic treatment with lithium has been shown to upregulate synaptosomal uptake of glutamate (Hokin et al. 1996, Bowden et al. 2000). Furthermore, chronic treatment with therapeutically relevant concentrations of lithium in cultured rat cerebellar, cortical and hippocampal neurons protected these cells against glutamate-induced excitotoxicity. The investigators reported that the protection could be attributed to inhibition of NMDA (N-methyl-D-aspartate) – receptor-mediated Ca^{2+} influx (Nonaka et al. 1998, Hashimoto et al. 2002).

This is plausible explanation indeed as NMDA-receptors are blocked under resting conditions by intracellular magnesium cations [intracellular magnesium concentrations range from 5 to 20 mM; 1–5% is ionized, the remainder is bound to proteins, negatively charged molecules and ATP (Jahnen-Dechent and Ketteler 2012)] and, once the surrounding plasma membrane area is depolarized by opening of AMPA (α-amino-3--hydroxy-5-methyl-4-isoxazole propionic acid) receptors, NMDA-receptors are activated by combined binding of two glutamate and two glycine molecules. NMDA-receptors activation serves as a functional marker of converging excitatory inputs, produces excitation over long period of time and an increased AMPA/NMDA throughput in critical neuronal circuits was suggested to represent the critical step in antidepressant action. Evidence for alteration of NMDA- and AMPA/kainate-receptors function has been intensively documented (Zarate et al. 2002, 2003, Kugaya and Sanacora 2005, Sanacora et al. 2008, Gray and McEwen 2013, Malhi et al. 2013).

Lithium and γ-aminobutyric acid (GABA) signaling cascades

GABA is the main inhibitory neurotransmitter in mammalian brain (Bowery et al. 1984, 1987, Sakaba and Neher 2003, Padgett and Slesinger 2010, Pinard et al. 2010) which plays a crucial role in modulating both dopamine and glutamate neurotransmission and hence it is also thought to play a key role in mood stabilization (Brambilla et al. 2003). Patients with mood disorders, in particular bipolar disorder, have diminished GABA-ergic neurotransmission (Kato 2008, Ng et al. 2009, Ghasemi and Dehpour 2011). Low GABA levels result in an increase in excitatory neurotransmission that leads to excitatory toxicity, and in turn causes apoptosis and cell loss (Rajkowska et al. 2001, Rajkowska 2002). In this context, lithium promotes the release of neuroprotective proteins and decreases the levels of pro-apoptotic proteins (Chuang et al. 2002). Lithium increases the level of GABA in the plasma and cerebrospinal fluid of humans as that of rats (Ahluwalia et al. 1981, Vargas et al. 1998, Brunello and Tascedda 2003). Interestingly, an increase in GABA in response to lithium reduces the level of glutamate, and this downregulates the NMDA-receptor (Ghasemi and Dehpour 2011).

Lithium, magnesium and trimeric G proteins

The average size of non-hydrated lithium cation (0.68 Å) is very close to the size of magnesium cation in crystal (0.65 Å). In aqueous solution, ionic radii of four- and six- water coordinate Li^+ is 0.60 and 0.79 Å, respectively (Mahler and Persson 2012). In aqueous solutions, Li^+ is more similar to Mg^{2+} than to Na^+ and K^+. When considering this similarity, one should bear in mind that ATP metabolism as well as normal neurological function and release of neurotransmitters are all magnesium dependent (Jahnen-Dechent and Ketteler 2012). Magnesium binds water molecules much tighter than calcium, potassium and sodium. Thus, the hydrated magnesium cation is hard to dehydrate. Its radius is ~400 times larger than its dehydrated radius. The difference between the hydrated and the dehydrated state is much larger than in sodium (~25-fold), calcium (~25-fold) or potassium (4-fold). Magnesium is surrounded by two hydration shells, whereas calcium has just one layer. If these two divalent cations need to fit into a structure of an enzyme or pore of ionic channel/transporter membrane protein, calcium will simply shed away its hydration shell and its dehydrated form will fit in. Magnesium, on the other hand, has to lose two layers of water molecules which is highly energy consuming.

It has been proposed that Li^+, a metal ion with an ionic radius similar to that of Mg^{2+} (Malarkey et al. 2008), can compete with Mg^{2+} for low affinity Mg^{2+}-binding sites in trimeric Gα subunits (Avissar et al. 1988, 1991, Mota de Freitas et al. 2006). Several of the seminal $G_i1α$ protein crystallographic experiments that showed one Mg^{2+}--binding site were conducted in the presence of very

high (up to 2 M) Li^+ concentrations (Coleman et al. 1994a, 1994b, Coleman and Sprang 1998), or were modeled on structures obtained in the presence of very high Li^+ concentrations (Sunahara et al. 1997, Tesmer et al. 1997). Hence, it is plausible that the Mg^{2+} at the low affinity Mg^{2+}-binding site was displaced by Li^+ and therefore not observed in the previously reported X-ray structures. Interestingly, in the only G protein X-ray structural study where two Mg^{2+}-binding sites were observed (Nicely et al. 2004), crystallization was conducted with polyethylene glycol rather than in high salt conditions. When another enzyme that has been shown to be susceptible to Li^+/Mg^{2+} competition at Mg^{2+}-binding sites, inositol monophosphatase (IMPase), was originally crystallized in the presence of high lithium sulfate concentrations (2.0 M), only one Mg^{2+}-binding site was observed (Bone et al. 1992, 1994); however, a recent crystallographic study of IMPase that used no Li^+ in the crystallization medium showed the presence of not one, but three Mg^{2+}-binding sites in the protein (Gill et al. 2005) giving further credence to the idea that weakly bound Mg^{2+} can be displaced by Li^+ in biomolecules.

Magnesium cations have a profound stimulatory effect on the interaction of many G protein coupled receptors with their agonists. The list of receptors that fall into this category includes β-adrenergic receptor (β-AR) (Bird and Maguire 1978, Williams et al. 1978), α2-adrenergic receptor (α2-AR) (Tsai and Lefkowitz 1978, 1979, Glossmann and Presek 1979), muscarinic acetylcholine receptor (mACh-R) (Wei and Sulakhe 1980, Hilf et al. 1989) and receptors for PGE1 (prostaglandin E_1) (Williams et al. 1978), opioids (Pasternak et al. 1975), dopamine (Sibley and Creese 1983) and chemotactic formyl peptide receptors (Gierschik et al. 1989, 1991). In most cases, the major effect of magnesium cations was an increase in receptor affinity for the agonist [β-AR (Bird and Maguire 1978, Williams et al. 1978) and α2-AR (Tsai and Lefkowitz 1978)], although an increase in the number of binding sites was also noticed [mACh-R (Glossmann and Presek 1979)].

Therefore, the effect of magnesium cations is diametrically opposite to the effect of guanine nucleotides, which are well known to reduce agonist affinity of all GPCRs. As the latter effect is due to a nucleotide-dependent functional and physical uncoupling of the receptor from G protein, it has been suggested that magnesium cations enhance agonist binding by stabilization of ternary, high-affinity complex H-R-G (complex hormone-receptor-G protein) which is necessary intermediate for hormonal stimulation of effector enzymes as well as guanine nucleotide-dependent transition of receptor from the high to low-affinity state (Bird and Maguire 1978, Tsai and Lefkowitz 1978, 1979, Williams et al. 1978). It was suggested that lithium interaction with G proteins may proceed as direct competition with magnesium ions bound to the low-affinity Mg2+-sites in Gα subunits (Malarkey et al. 2008). Mg2+-binding is known to be essential for agonist-stimulated GDP-GTP exchange reaction proceeding in guanine-nucleotide binding domain of Gα subunits, namely, for the fast change of Gα-GTP conformation (Gilman 1987, Higashijima et al. 1987a, 1987b, 1987c). Activation of G proteins by guanine nucleotides changes the protein conformation. Concomitant with this structural change is an increase in the intensity of fluorescence of tryptophan residues. Both GTPγS and GTP can cause this change, suggesting that a similar alteration in protein structure is caused by the different nucleotides. When GTP is added to GDP-containing G_o, there is a slow increase in the intensity of tryptophan fluorescence as GDP dissociates and GTP then binds. After GDP has been replaced with GTP, the addition of Mg^{2+} causes a rapid increase in fluorescence intensity, reflecting the formation of $G_o\alpha$-GTP-Mg^{2+}. Unlike the complex formed in the presence of GTPγS, the GTP containing form of the protein is transient, because GTP is hydrolyzed to GDP and P_i in the presence of Mg^{2+}.

Further down-stream, lithium was found to decrease activity of numerous signaling proteins which are primarily regulated by G proteins. (Avissar and Schreiber 2006, Gonzalez-Maeso and Meana 2006, Can et al. 2014). Lithium was found to inhibit adenylyl cyclase activity (Avissar et al. 1988, Mork and Geisler 1989, Newman et al. 1990, Minadeo et al. 2001, Srinivasan et al. 2004), turn-over of neurotransmitter-stimulated phosphatidylinositol metabolism (Jope and Williams 1994) and activity of inositol-1-monophosphatase (Wang and Friedman 1999). As c-AMP- and IP_3-dependent cascades are regulated by different G protein families (G_s, G_i, G_o, G_q/G_{11}), the effect of chronic lithium on functional coupling between serotonin (5-HT) receptors and G proteins was investigated in details (Wang and Friedman 1999). Incubation of rat cortical membranes with 5-HT increased [^{35}S]GTPγS binding to $G_s\alpha$, $G_i\alpha$, $G_o\alpha$ and $G_q\alpha$ proteins. Six weeks but not one week of lithium treatment reduced the 5-HT-stimulated [^{35}S]GTPγS binding to $G_s\alpha$, $G_i\alpha$ and $G_o\alpha$ by 75–85%, whereas 5-HT stimulated [^{35}S]GTPγS binding to $G_q\alpha$ was decreased by 38%. No changes of Gα protein levels were noted in lithium treated rats. Increases in [^{35}S]GTPγS binding to Gα proteins by 5-HT were also inhibited by 0.5–2 mM lithium chloride added *in vitro* to assays mixture. Rubidium and cesium did not change 5-HT-stimulated G protein activity. The inhibitory effect of lithium on 5-HT-stimulated [^{35}S]GTPγS binding to $G_s\alpha$ and $G_q\alpha$ was completely removed by 2.4 mM $MgCl_2$; this concentration of $MgCl_2$ competed out the effect of lithium on $G_i\alpha$ and $G_o\alpha$ by 50%. These results indicated that lithium interferes with receptor-G protein coupling via a Mg^{2+}-dependent mechanism.

Receptor-mediated G protein activation and changes in the amount of different Gα subunits were further examined in frontal cortical membranes obtained from postmortem

brains of bipolar affective disorder subjects and from age-, sex-, and postmortem interval-matched controls (Friedman and Wang 1996). Stimulation of cortical membranes with serotonin, isoproterenol, or carbachol increased [^{35}S]GTPγS binding to specific Gα proteins in a receptor-selective manner. The abilities of receptor agonists to stimulate the binding of [^{35}S]GTPγS to the Gα proteins was enhanced in membranes from bipolar brains. Immunoblot analyzes showed increases in the levels of both short and long (45 and 52 kDa) isoforms of $G_s\alpha$, but no changes in the amounts of $G_i\alpha$, $G_o\alpha$, $G_z\alpha$, $G_{q/11}\alpha$ or Gβ subunit proteins in membrane or cytosol fractions of bipolar brain homogenates. Pertussis toxin (PTX)-activated ADP-ribosylations of $G_i\alpha$ and $G_o\alpha$ were enhanced by ≈80% in membranes from bipolar compared with control brains. Serotonin-induced, magnesium-dependent reduction of PTX-mediated ADP-ribosylation of $G_i\alpha$ and $G_o\alpha$ in cortical membranes from bipolar brains was greater than that observed in controls, providing further evidence for enhanced receptor-G protein coupling in bipolar brain membranes. In addition, the amounts of Gβ that co-immunoprecipitated with the Gα proteins were also elevated in bipolar brains. The data show that in bipolar brain membrane there is enhanced receptor-G protein coupling and an increase in the trimeric state of the G proteins. These changes may contribute to produce exaggerated transmembrane signaling and to the alterations in affect that characterize bipolar affective disorder.

Over the years, the evidence for "negative", inhibitory effect of lithium on G protein function was strengthened and considered to be involved in the pathogenesis as well as therapy of mood disorders (Schreiber and Avissar 2007). The related hypotheses suggest that G proteins are hyper-functional in mania and stabilized by lithium treatment (Schreiber and Avissar 1991, el-Mallakh and Wyatt 1995). Numerous studies have provided evidence for hyper-function of G proteins and their abnormal quantities in postmortem tissues of bipolar patients compared to healthy individuals (Schreiber et al. 1991, Young et al. 1991, Friedman and Wang 1996, Gonzalez-Maeso and Meana 2006). Determination of (responding) G protein levels and activities was tested as biochemical marker of a given type of mental disorder (Avissar and Schreiber 2002).

Genetic background of lithium effects was mostly studied in context of heterogeneity and pathological mutations of serotonin, dopamine and glutamate receptors and of enzymes regulating the synthesis and degradation of secondary messengers cAMP and IP_3. Genes encoding protein kinase C (PKC), Brain Derived Neurotropic Factor (BDNF) and glycogen synthase kinase 3β (GSK-3β) were recognized in this respect (Rybakowski 2013). In one of the latest publications oriented to analysis of candidate genes participating in the pathogenesis of mood disorders, OPRK1 encoding κ_1–subtype of opioid receptors was identified (Deo et al. 2013).

Opioid receptors and mood disorders

There are a numerous studies that link the endogenous opioid system with major psychiatric disorders and suicide (Scarr et al. 2012). It has been clearly established that the μ-opioid receptors are altered in people with affective disorders who died as a result of suicide (Gross-Isseroff et al. 1990, Gabilondo et al. 1995). In patients with bipolar disorder, the higher levels of specific [^{3}H]DAMGO ([D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin) binding were detected in ventral anterior cingulate gyrus (BA24) when compared with control patients (Scarr et al. 2012). The role of δ-opioid receptor signaling cascade was in turn found to participate in the regulation of mood and emotional states, since the activation of δ-opioid signaling, according to preclinical studies, was reflected in generating of an enormous antidepressant-like effects (Jutkiewicz 2006).

It is known, that lithium interacts with opioid system and even very low lithium doses can effectively regulate opioid transmission (Dehpour et al. 1995, Honar et al. 2004, Banafshe et al. 2012). Lithium and morphine have the opposite effect on transmembrane signal control systems and lithium is able to influence both acute and chronic effects of morphine (Dehpour et al. 1995, Honar et al. 2004). Lithium may both enhance and attenuate opioid-induced antinociception (Dehpour et al. 1994), morphine-induced hyperactivity (Carroll and Sharp 1971) and it significantly inhibits severity of withdrawal syndrome and development of physical dependence (Dehpour et al. 1995) etc.

Chronic administration to lithium stimulates release of hypothalamic opioid peptides in the rat brain (Kurumaji et al. 1988). This effect was found to be caused by permanent decrease in activity of inhibitory opioid auto-receptors and G proteins of G_i/G_o family (Burns et al. 1990). Blockage of these auto-receptors by μ-opioid receptor antagonist naloxone causes the release of all three opioid peptides – beta-endorphin, met-enkephalin and dynorphin, and it does not occur after concomitant administration of naloxone together with lithium. Chronic administration to lithium has no effect on basal level of opioid peptides, but prevents their release induced by naloxone. It was also reported that chronic administration of lithium increases stress-induced hypoalgesia (Teixeira et al. 1995) and increases the expression of μ-opioid receptors in the rat brain (de Gandarias et al. 2000).

Lithium and opioid receptors

The interaction of monovalent cations with signaling cascades initiated by opioid receptors (OR) was studied since the very early days of GPCR-oriented research. The stereo-specific binding of OR agonists [^{3}H]dihydromorphine and [^{3}H]oxymorphine to brain membranes was found to

be inhibited by increasing concentrations of NaCl and to a less extent by LiCl (Pert et al. 1973, Pert and Snyder 1974, Pasternak and Snyder 1975). Other ions, potassium, rubidium, and cesium were not effective ($Na^+ \gg Li^+ > K^+ \approx Rb^+ \approx Cs^+$). On the contrary, antagonist binding to OR was affected in a positive manner. Binding of the antagonist [^{3}H]naloxone was increased, again in the order $Na^+ \gg Li^+ > K^+ \approx Rb^+ \approx Cs^+$. Original data of Pert and Snyder (Pert and Snyder 1974) were confirmed and extended by studies on membranes prepared from the whole guinea pig brain and cerebellum (Paterson et al. 1986).

Later studies of interaction of sodium cations with δ-OR using the known amino acid sequence of δ-OR indicated that a conserved aspartic acid 95 in the second TM region is critical for Na^+ regulation of agonist binding (Kong et al. 1993). Recent data based on the crystal structure of the μ-OR in a complex with the irreversible antagonist morphinan (Manglik et al. 2012) and mouse δ-OR with the antagonist naltrindol (Granier et al. 2012) at 2.8–3.3 Å resolution indicated that these antagonists bind within a large solvent-exposed pocket. This extra large "water-accessible space" of the antagonist binding site of OR is a characteristic feature of this type of receptors and differs from most other GPCRs including β2-AR (Filizola and Devi 2012). The binding pocket of opioid receptors can be divided into two distinct regions. The bottom or inner part of this pocket is highly conserved among OR whereas the upper part (exposed to extracellular aqueous space) contains divergent residues that confer subtype selectivity.

The effect of sodium, potassium and lithium on δ-opioid receptor ligand binding parameters and coupling with the cognate G proteins was also tested in model HEK293 cell line stably expressing PTX-insensitive δ-OR-$G_i1\alpha$ ($C^{351}I$) fusion protein (Vosahlikova et al. 2014). Agonist [^{3}H]DADLE ([D-Ala^2, D-Leu^5]-enkephalin) binding was decreased in the order: $Na^+ \gg Li^+ > K^+ > (^+)$NMDG (N-methyl-D-glucamine). When plotted as a function of increasing NaCl concentrations, the binding was best-fitted with a two-phase exponential decay considering the two Na^+-responsive sites (r^2=0.99). High-affinity Na^+-sites were characterized by K_d =7.9 mM and represented 25% of the basal level determined in the absence of ions. The remaining 75% represented the low-affinity sites (K_d=463 mM). Inhibition of [^{3}H]DADLE binding by lithium, potassium, and ($^+$)NMDG proceeded in low-affinity manner only. Surprisingly, the affinity/potency of DADLE-stimulated [^{35}S]GTPγS binding was increased in the reverse order: $Na^+ < K^+ < Li^+$. This result was demonstrated in PTX-treated as well as PTX-untreated cells and is therefore valid for both $G_i1\alpha$ ($C^{351}I$) within the δ-OR-$G_i1\alpha$ fusion protein and endogenous G proteins of Gi/Go family present in HEK293 cells.

Noticeably, the K_d=7.9 mM of high-affinity sites for Na^+ determined in δ-OR-$G_i1\alpha$ ($C^{351}I$) was close to allosteric interaction constant K_B=13.3 mM determined by Fenalti and others (2014). Similarly to our study, these authors performed [^{3}H]DADLE binding experiments in media containing up to 400 mM NaCl; at 100 mM concentration of chloride salts of different ions, the inhibition of [^{3}H]DADLE binding to BRIL-δ-OR (ΔN/ΔC) [human δ-opioid receptor (residues 36–338) with an amino-terminal BRIL (apocytochrome b_{562}RIL) fusion protein] was significant for sodium only, however, Li^+ represented the second most effective ion.

As mentioned above, the early studies of rat brain homogenates indicated a differential sodium regulation of ligand binding to the three major OR subtypes, in spite of their high degree of amino acid sequence similarity. At physiological concentrations, sodium ions were found to decrease the level of binding of agonists, but not antagonists to the μ-opioid receptor (μ-OR) (Pert et al. 1973, Pasternak and Snyder 1975). While similar allosteric effects were confirmed for several, albeit not all different family A GPCRs (Katritch et al. 2014), the possibility that sodium differentially affects the binding of an agonist to the three major OR subtypes was also raised, with 65% agonist binding inhibition seen in μ-OR and δ-OR, but only 20% inhibition observed in κ-opioid receptor (κ-OR) (Werling et al. 1986).

Differences in allosteric modulation of individual subtypes of OR, μ-, δ- and κ-OR by sodium cations were recently characterized by MD (molecular dynamics) simulations with the aim to distinguish whether sodium accesses the allosteric site (in different OR subtypes) via the similar or different pathways (Shang et al. 2014). Rapid sodium permeation was observed exclusively from the extracellular milieu, and following the similar binding pathways in all three ligand-free OR systems, notwithstanding extra densities of sodium observed near nonconserved residues of κ-OR and δ-OR, but not in μ-OR. These differences might be responsible for the differential increase in antagonist binding affinity of μ-OR by sodium resulting from specific ligand binding experiments in transfected cells. On the other hand, sodium reduced the level of binding of subtype-specific agonists to all OR subtypes.

Lithium – sodium competition for orthosteric and allosteric sites of GPCR

In the late 1980s and early 1990s, the concept of constitutive GPCR activity was developed. This concept assumes that receptors exist in an inactive (R) and an active (R*) state and that they isomerize between these two states (Lefkowitz et al. 1993). The equilibrium between these two states is different for any given receptor, and when agonist-independent (constitutive) R to R* isomerization is sufficiently high, the measurable basal G protein and effector activation is detected (Seifert and Wenzel-Seifert 2002).

This basal G protein and effector activity can be reduced by inverse agonists that stabilize the R state of receptor molecule.

Na^+ can effectively reduce constitutive GPCR activity and its action on several GPCR including β2-adrenergic and chemoattractant receptors allowed formulating the pharmacological concept that Na^+ acts like a universal allosteric modulator of GPCR (Seifert and Wenzel-Seifert 2001). This pharmacological concept was confirmed by the recent studies showing crystal structures of GPCRs bound to Na^+. The crystal structures show that the Na^+ binds in an allosteric binding site near the highly conserved Asp2.50 (Liu et al. 2012, Fenalti et al. 2014, Katritch et al. 2014, Miller-Gallacher et al. 2014). Based on the MD simulation data, it can be assumed that the monovalent cations bind to the allosteric site by coming from the extracellular side. When following the binding trajectory, the cations pass the orthosteric ligand binding site (Selent et al. 2010, Yuan et al. 2013, Wittmann et al. 2014).

The most detailed ideas about modulation of GPCRs by monovalent cations were recently presented by Strasser and others (2015). Based on crystal structures of the human histamine H1 receptor (Shimamura et al. 2011), human dopamine D3 receptor (Chien et al. 2010), human adenosine A2A receptor (Liu et al. 2012) and human δ-opioid receptor (Fenalti et al. 2014), these authors performed MD simulations of GPCR embedded in a lipid bilayer and surrounded by water molecules and ions with the aim to observe its conformational dynamics on a molecular level. These studies allowed delineating the binding pathways for ions and binding and unbinding of water molecules approaching GPCR from extracellular side of plasma membrane into an orthosteric and allosteric binding sites, respectively.

The calculation of interaction energy (ΔG) at an intersecting plane through the channel between the ortho- and allosteric binding site of human histamine H3 receptor (hH3R) showed that there are two preferred areas for cations: first, around the highly conserved Asp3.32 in orthosteric site and second, around the highly conserved Asp2.50 in the allosteric binding site. With increasing size of the cation in the series $Li^+ \rightarrow Na^+ \rightarrow K^+ \rightarrow Rb^+ \rightarrow Cs^+$, the energetically favoured area decreases. Additionally, in the same series, transition of the cation through the connecting channel becomes energetically more and more disfavoured.

Water molecules are important in interaction of a Na^+ with the allosteric binding site (Liu et al. 2012, Katritch et al. 2014) and previous modeling studies showed that water molecules connect the orthosteric and the allosteric binding site (Wittmann et al. 2014). While the preferred binding area of the analyzed cations is very similar for the orthosteric binding site, there are obvious differences in the preferred binding for Li^+ and Na^+ on the one hand and K^+, Rb^+ and Cs^+ on the other hand: while Li^+ and Na^+ bind deeper into the allosteric pocket, K^+, Rb^+ and Cs^+ bind preferably at the area between the binding channel and the upper part of the allosteric binding site. Here, the hydration by water molecules or coordination by amino acid side chains and the preferred hydration number play a role. These differences lead to distinct signatures of cation binding in the allosteric site. Consequently, binding of different monovalent cations to the allosteric site may result in distinct interaction networks within the receptor, and these different interaction patterns may result in different receptor conformations.

Thus, in similarity with conventional GPCR ligands, GPCR-specific structure-activity relationships for various cations are emerging (Strasser et al. 2015). Based on these data, it can be suggested that there is a rising preference for binding of a monovalent cation in the Hofmeister (1888) series $Cs^+ \rightarrow Rb^+ \rightarrow K^+ \rightarrow Na^+ \rightarrow Li^+$. This trend regarding the basal GTP hydrolysis was also shown previously by experimental studies of hH3R for $K^+ \rightarrow Na^+ \rightarrow Li^+$ (Schnell and Seifert 2010).

Lithium dosing and toxicity

Lithium salts, mostly in the form of lithium carbonate (also acetate, citrate, gluconate or sulfate), are administered as an oral tablets [in daily dose 0.4 to 2.0 g/day of lithium carbonate depending on age and bodyweight (Oruch et al. 2014)]. Following oral administration is lithium rapidly and completely absorbed from gastrointestinal tract (Suwalsky et al. 2007, Oruch et al. 2014). The effectiveness of lithium is dependent on dose and reliably correlates with serum concentration (Grandjean and Aubry 2009a). The typical therapeutic range in blood is 0.5 to 1.2 mM, however, the higher concentrations are needed for the treatment of acute mania (Grandjean and Aubry 2009a, Young 2009, Oruch et al. 2014). The doses above 1.5 mM have to be regarded as toxic (Young 2009). Toxicity associated with lithium treatment is highly prevalent as 75 to 90% of patients have signs or symptoms of toxicity during their treatment (Mallinger et al. 1990, 1997, Webb et al. 2001, Gill et al. 2003). The occurrence of toxicity is related to the serum concentration of lithium. Mild toxicity appears at levels up to 2.5 mM, and life-threatening effect is manifested at levels above 3.5 mM (Peces and Pobes 2001, Borras Blasco et al. 2005); the patients with concentrations as high as 6 mM (Dupuis et al. 1996), and even 9.6 mM (Jaeger et al. 1993) lithium serum levels following acute intoxication were reported.

The overall concentration of lithium in the brain is only poorly correlated with serum concentration and brain/serum ratios based on ^7Li magnetic resonance spectroscopy (^7Li MRS) were determined in 0.4–1.0 range (Soares et al. 2000).

In addition to its proven effectiveness, however, lithium has particularly problematic side effects associated with a number of difficulties and risks. It has narrow therapeutic

window and overdosing is therefore a risky factor of proper therapy but even the correct dosage can lead to undesirable side effects (Can et al. 2014). Moreover, effect of lithium, especially when used as antidepressant, is evident after at about 2 months, which precludes its use when a fast-acting pharmacological treatment is necessary (Can et al. 2014). In the treatment of bipolar depression, the disadvantage of lithium is due to the delayed effect of 6–8 weeks, compared with 6–10 days in the treatment of acute mania (Gershon et al. 2009, Grandjean and Aubry 2009b).

Up-to-date review of mood stabilizers clinical management was performed last year by Murru and others (2015). According to this study mood stabilizers (including lithium) have different tolerability profiles and are eventually associated to cognitive, dermatological, endocrine, gastrointestinal, immunological, metabolic, nephrogenic, neurologic, sexual and teratogenic adverse effects. Long-term lithium treatment indicates a possibility of nephrotoxic effects of this ion (Rybakowski et al. 2012) and after many years of treatment renal impairment may occur. Moreover lithium is reabsorbed in the kidney after the glomerular filtration. It can be assumed that therapeutic outcome of lithium is related with the functional expression of sodium-phosphate cotransporter in the kidney which contributes to reabsorption of more than 65.9% (Uwai et al. 2014). Lithium-induced renal toxicity is mainly manifested as a nephrogenic diabetes insipidus (NDI). NDI, which can be congenital or acquired (for example lithium therapy), results from failure of the kidney to respond to vasopressin (Sands et al. 2006). On the other hand long-term, low-dose (0.2–0.4 mmol/l) lithium treatment does not impair renal function in the elderly (Aprahamian et al. 2014) and end-stage renal disease is a very rare complication. Long-term lithium treatment is except of a decline of renal function also associated with hyperthyroidism and hypercalcaemia (Shine et al. 2015). Common acute adverse effects of lithium as nausea, dysguesia, vomiting, loss of appetite or diarrhea are usually transient and manageable with dose reduction. Concerning dermatological problems the most common are acne and psoriasis. Mild cognitive symptoms are frequent with higher plasma levels of lithium but the real impact of therapeutic blood levels on cognitive impairments in bipolar disorder has not been clarified (López-Jaramillo et al. 2010). Treatment with lithium may induce weight gain and sexual dysfunction; the teratogenic risk is relatively low in absolute terms (Murru et al. 2015).

Lithium and membrane lipids; biophysical studies of direct interaction of ions with model lipid bilayers and natural membranes

The influence of physiologically relevant ions (Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+}) on model lipid membranes was extensively studied in the past (Böckmann et al. 2003, Vacha et al. 2009). Other ions, such as Li^+, Cs^+, NH_4^+, Ba^{2+}, La^{3+}, F^-, Br^-, I^-, NO_3^-, and SCN^-, were also investigated (McLaughlin et al. 1978, Garcia-Celma et al. 2007), but, because the specificity of ionic effects were more pronounced for anions than for cations, the number of experimental data on analysis of cationic effects were sparser (Tatulian 1987, Clarke and Lupfert 1999, Kunz et al. 2004, Garcia-Celma et al. 2007). However, the conclusion drawn from all these studies was unequivocal: the strongest effects were observed for ions characterized by a high charge density: bivalent cations Mg^{2+}, Ca^{2+} and Li^+ (Pabst et al. 2007, General discussion 2013).

Since some of naturally occurring lipids are anionic, adsorption of cations to natural lipid membranes is stronger than to electrically neutral model membranes. This is due to the coulombic attraction between positively charged cations and negatively charged head-groups in the inner leaflet of natural lipid bilayer. For example, in mixed POPC (1,2-palmitoyl-oleoyl-*sn*-glycero-3-phosphocholine)/ POPS (1,2-palmitoyl-oleoyl-*sn*-glycero-3-phosphoserine) (4:1, mol:mol) lipid bilayers, which are often used as a model of inner leaflet of a plasma membrane enriched in PS, adsorption of cations was found to follow the reversed Hofmeister series: $Na^+ > K^+ > Cs^+$ (Eisenberg et al. 1979).

Most lipids exhibit similar chemical properties in the presence of alkali metal ions, with one exception – Li^+. Interaction of lithium with phosphatidylserine (PS) bilayer, unlike interaction of other monovalent ions, leads to the isothermal crystallization and production of crystalline lipid complexes, Li^+-PS (Hauser and Shipley 1981, 1983). PS is the main acidic, negatively charged phospholipid present in all eukaryotic biomembranes, it is preferentially localized in inner leaflet of plasma membrane and its content is especially high in neuronal membranes. Accordingly, the structure of model dipalmitoylphosphatidylserine (DPPS) bilayer was strongly altered by lithium addition: DPPS membrane was transferred from disordered to gel state and became more hydrated at lipid-water interface (Lopez Cascales and Garcia de la Torre 1997). Lithium exhibited the strong affinity for lipid phase and displaced the sodium ions towards the water space. Binding of Li^+ and Na^+ to DPPS was associated with dehydration of both ions. The decrease of water molecules in the first hydration shell of these ions was compensated by lipid oxygen's.

Electrostatic interaction of lowconcentrations of Li^+ (<1 mM) with polar head-group region of phosphatidylcholine located in the outer monolayer of the erythrocyte membrane was suggested to represent the primary factor inducing the pathological change of intact red blood cell into an "echynocytotic type" characterized by formation of blebs and protuberances on the cell surface (Suwalsky et al. 2007).

More recent publications using computer simulations showed that adsorption of Na^+ to negatively charged membranes often leads to complexation of up to 4 lipid

molecules, but the exact binding sites were dependent on the force field (Pandit et al. 2003, Porasso and Lopez Cascales 2009, Broemstrup and Reuter 2010). Addition of 20 mol% of POPS to zwitterionic POPC strengthened the adsorption of monovalent ions to lipid bilayer with the order of: Na^+>K^+>Cs^+ (Jurkiewicz et al. 2012). The time-resolved fluorescence solvent relaxation studies of interaction of sodium, potassium and cesium chlorides with POPC/POPS bilayer by Laurdan GP indicated the decrease of both mobility and hydration of lipid carbonyls. Molecular dynamics simulations were best interpreted as the deep penetration of ions down to the glycerol level of the lipid bilayer and pairing with oxygen atoms of carbonyl groups. Monovalent ions were found to bridge the neighboring lipids forming the clusters of up to 4 lipid molecules. This type of bridging decreased the average lipid area within the plain of membrane, thickened the membrane transversally, caused the rising of lipid head-groups and hindered lipid dynamics. Importantly, all these effects were found to follow the same, Hofmeister ordering as the cationic adsorption to the bilayer: Na^+>K^+>Cs^+ (Jurkiewicz et al. 2012).

Analysis of interaction of lithium, sodium, potassium and cesium with plasma membranes isolated from HEK293 cells by Laurdan GP indicated the low-affinity type of interaction only proceeding in the order: Li^+>Na^+>K^+>Cs^+ (Vosahlikova et al. 2014). The interaction of ions with negatively charged POPC/POPS and POPC/POPS/cholesterol vesicles decreased in the same order: Li^+>Na^+>K^+>Cs^+ and was interpreted as decreased hydration and mobility of the polar head-group region of lipid bilayer. The same order of efficiency of monovalent cations in both types of membranes (HEK293 membranes and POPC/POPS vesicles), which was clearly related to the surface charge density of a given cation, represented a contribution to biophysical studies of specific ionic effects related to the early works of Franz Hofmeister (Hofmeister 1888). The so-called Hofmeister series of ions have been found to be similar for many different phenomena observed at complex macromolecular, polymeric and biological interfaces. However, at present time, there is a growing evidence for the complex origin of these effects (General discussion 2013) as an experimental systems have been identified in which the Hofmeister series can be partly or completely reversed (Parsons et al. 2010, Schwierz et al. 2010).

In this context, the role of counter anions has to be considered. The iodide anions (I^-), being more hydrophobic than Cl^- and Br^-, were found to penetrate deeply into the membrane bilayer (Jurkiewicz et al. 2011). Importantly, iodide salts of monovalent cations were more efficient than chloride salts when modulating agonist binding and G protein coupling of β2-adrenergic, chemokine CXCR4 and histamine H3 receptors (Seifert 2001, Kleemann et al. 2008, Schnell and Seifert 2010). Data of Vosahlikova and others (2014) supported these results as the inhibition of agonist [^{3}H]DADLE binding to δ-OR-G_i1α (C^{351}I) fusion protein stably expressed in HEK293 cells was increased in the order: NaCl<NaBr<NaI (Fig. 2A). The same order of efficacy was found for inhibition of the basal and DADLE-stimulated [^{35}S]GTPγS binding by these salts (Fig. 2B).

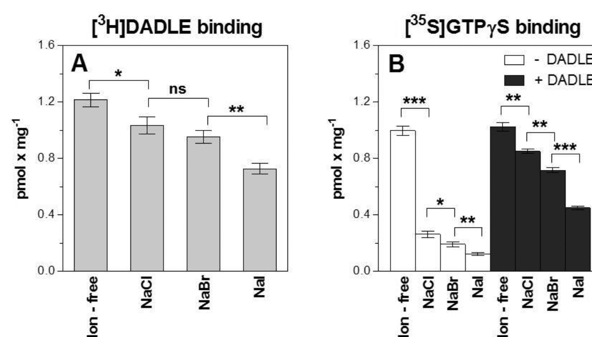

Fig. 2. Decrease of [^{3}H]DADLE (A) and [^{35}S]GTPgS binding (B) by NaCl, NaBr, NaI (Fig. 4 in Vosahlikova et al. 2014). [^{3}H]DADLE and [^{35}S]GTPγS binding assays were performed in ion-free and 145 mM NaCl, NaBr and NaI containing media. P2 membrane fraction isolated from PTX-untreated HEK293 cells stably expressing δ-OR-G_i1α (C^{351}I) fusion protein was used. Numbers represent the means ± SEM of 3 binding assays performed in triplicate. The same membrane preparation was used in all assays. Data were analyzed by one-way ANOVA followed by Bonferroni's Multiple Comparison Test (ns, $p>0.05$; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$).

The effect of therapeutic concentrations of lithium on membrane lipids prepared from natural cells and tissues

Lopez-Corcuera, in his work from 1988 (Lopez-Corcuera et al. 1988), examined the effect of prolonged influence of therapeutic concentrations of lithium salts on lipid composition and biophysical properties of synaptosomal plasma membrane vesicles (SV) prepared from rat brain. Fluorescence polarization of lipophilic (DPH, 1,6-difenyl-1,3,5-hexatriene) and charge-sensitive (ANS, 1-anilinonaphthalene-8-sulfonic acid) probes was used to study membrane lipid structure. Steady-state polarization of DPH was significantly lower in SV prepared from lithium treated animals. Decrease of DPH polarization was due to the increase of S-order parameter. Lithium-treatment was also found to change fluorescence intensity of ANS bound to surface of SV and increase the content of unsaturated fatty acids in membrane phospholipids. The cholesterol-phospholipid ratio was unchanged.

The effect of the long-term administration of different antidepressants on composition of rat brain lipids was studied in detailed manner by Fisar and others (2005). Significant decrease in content of PE (phosphatidylethanolamine) was

noticed after administration of maprotiline, citalopram and moclobemide. Membrane cholesterol level was decreased by desipramine but increased after citalopram and lithium. Electroneutral phospholipids were decreased after administration of all tested antidepressants with exception of desipramine. Decrease of PS was noticed after maprotiline and desipramine; phosphatidylinositol was decreased by lithium treatment. Statistically significant negative correlation between cholesterol and electroneutral phospholipids was clearly identified. Membrane microviscosity was only slightly decreased by desipramine and increased by citalopram.

Of the many hypotheses regarding the action of mood stabilizers in bipolar illness, "arachidonic acid (AA) cascade" hypothesis was reviewed in detailed manner (Rapoport et al. 2009). This hypothesis is based on evidence that chronic administration of lithium, carbamazepine, valproate or lamotrigine to rats down-regulated AA turnover in brain phospholipids and decreased formation of prostaglandin E2 and expression of AA-cascade enzymes – cytosolic phospholipase A2, cyclooxygenase-2 and/or acyl-CoA synthetase. The changes were selective for AA, since the brain metabolism of docosahexaenoic and palmitic acids was not unaffected. Topiramate, ineffective in bipolar illness, did not modify the rat brain AA cascade.

Down-regulation of the AA cascade by the mood stabilizers corresponded to inhibition of AA neurotransmission by dopaminergic D2-like and glutamatergic NMDA-receptors. Unlike the mood stabilizers, antidepressants that increase switching of bipolar depression to mania, up-regulated the rat brain AA cascade. These observations suggested that the brain AA cascade is a common target of mood stabilizers and bipolar symptoms, particularly in mania, are associated with an up-regulated AA cascade and excess AA signaling via D2-like and NMDA-receptors (Rapoport et al. 2009).

The thorough and comprehensive review of the role of brain n-3 polyunsaturated fatty acids (PUFA), glycerolipids, glycerophospholipids and sphingolipids in induction of the major depression and anxiety disorders was recently presented by Muller and others (2015). The authors conclude that large number of observational and interventional studies convincingly indicated the beneficial effects of n-3 long-chain PUFAs in the treatment of depression and anxiety. However, more research is needed to determine the most efficient type, dose and duration of n-3 PUFA supplementation; the most efficient treatment may be limited to specific subgroups of patients only. It should also be noted that from current mechanistic research it is not clear whether PUFA effects in depression and anxiety are mediated by changing the properties of plasma membrane itself or by altered levels of PUFA-derived lipid signaling molecules (Wilson and Nicoll 2002, Chevaleyre et al. 2006, Regehr et al. 2009).

CONCLUSIONS

Lithium is still the most effective therapy for depression. It "cures" a third of the patients with manic depression, improves the lives of about a third, and is ineffective in about a third. Anticonvulsants valproate, carbamapazine, and lamotrigene may be useful in patients that do not respond to lithium (Young 2009). Even though there is a decline in the use of lithium, it is still recommended as the first choice for dealing with bipolar disorder according to all of the current medical handbooks (Grandjean and Aubry 2009b). Lithium is a typical mood stabilizer and has in this group of drugs a unique position. It has both the antimanic and extraordinary antidepressant activity; the antimanic effect being more pronounced than antidepressant. Unlike mood stabilizers that were originally indicated in the treatment of other diseases (anticonvulsants for treating epilepsy and antidepressants to treat schizophrenia), lithium is almost entirely effective in the treatment of mood disorders (Can et al. 2014). Moreover, there is evidence that lithium reduces the high risk of suicide in patients with bipolar disorder (Grandjean and Aubry 2009b, Kovacsics et al. 2009, Manchia et al. 2013).

The effective dose range for lithium is 0.6–1.0 mM in serum and >1.5 mM may be toxic. Serum lithium levels of 1.5–2.0 mM have mild and reversible toxic effects on kidney, liver, heart, and glands. Serum levels of >2 mM may be associated with neurological symptoms, including cerebellar dysfunction. Prolonged lithium intoxication >2 mM can cause permanent brain damage (Young 2009).

Although the concentrations at which Li^+ affects GPCR function *in vitro* are much higher than the therapeutic plasma concentrations in patients (≈1 mM), it cannot be excluded that Li^+ interacts with GPCRs *in vivo*. Limitation of the studies conducted with the effect of Li^+ on GPCRs *in vitro* was the fact that Li^+ was studied alone and not in competition with Na^+ or K^+ (Gierschik et al. 1991, Seifert 2001). In similarity with conventional GPCR ligands, GPCR-specific structure-activity relationships for various cations are emerging at present time (Strasser et al. 2015). It can be suggested that there is a rising preference for binding of a monovalent cation in the so-called Hofmeister (1888) series $Cs^+ \rightarrow Rb^+ \rightarrow K^+ \rightarrow Na^+ \rightarrow Li^+$. This trend regarding the basal level of GTP hydrolysis by G proteins was also shown in studies of hH3R: $K^+ \rightarrow Na^+ \rightarrow Li^+$ (Schnell and Seifert 2010).

As recently reviewed by Can and others (2014), the first usage of lithium was in the form of bromide salt: "Latterly I have used the bromide of lithium in cases of acute mania and have more reason to be satisfied with it than with any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present. The rapidity with which its effects are produced renders it specially applicable in such cases. The doses should be large – as high as sixty grains even more

– and should be repeated every two or three hours till be produced, or at least till half a dozen doses be taken. After patient has once come under its influence, the remedy should be continued in smaller doses, taken three or four times in the day" (Hammond 1871, p. 381).

This clinical report, formulated 144 years ago, is compatible with the observations indicating that bromide (Br^-) and iodide (I^-) anions, being more hydrophobic than Cl^-, were found to penetrate deeply into the membrane bilayer (Jurkiewicz et al. 2011). Importantly, iodide salts of monovalent cations were more efficient than chloride salts when modulating agonist binding and G protein coupling of β2-adrenergic, chemokine CXCR4 and histamine H3 receptors (Seifert 2001, Kleemann et al. 2008, Schnell and Seifert 2010). Data of Vosahlikova and others (2014) supported these results as the inhibition of agonist [^{3}H]DADLE binding to δ-OR-$G_i1α$ ($C^{351}I$) stably expressed in HEK293 cells was increased in the order: NaCl<NaBr<NaI (Fig. 2A). The same order of efficacy was found for inhibition of the basal and DADLE-stimulated [^{35}S]GTPγS binding by these salts (Fig. 2B).

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