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Review

Antiapoptotic action of lithium and valproate

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Abstract:
Lithium and valproate (VPA) have been the most widely prescribed mood stabilizers for the therapy of bipolar disorders (BD) for more than 50 years. However, the precise molecular mechanism of their pharmacological activity is not fully known. Recent studies have suggested that both drugs exert antiapoptotic effects. This review focuses on the influence of lithium and VPA on intracellular apoptotic signaling pathways. The active sites, which are implicated in mediating their action, have been described. It has been found that both drugs block the key proapoptotic molecules (GSK-3β, caspase cascades) and enhance survival pathways (ERK1/2 and Bax proteins). The potential significance of the reported antiapoptotic effects has been discussed.

Key words:
lithium, valproate, pro- and antiapoptotic factors

Abbreviations: ALS – amyotrophic lateral sclerosis, Bax – proapoptotic proteins, Bcl-2, Bcl-xl – antiapoptotic proteins, BD – bipolar disorders, ERK – extracellular signal regulated protein kinases, FAS – cell surface receptor that transduces apoptotic signal, GSK-3β – glycogen synthase kinase 3β, HSP70 – heat shock protein 70, IP-3 – phosphate inositol, LDH – lactate dehydrogenase, MAPK – mitogen-activated protein kinase, MARCS – myristoylated alanine-rich kinase C substrate, MCAO – middle cerebral occlusion, NAIP – neuronal apoptosis inhibitory protein, NMDA – N-methyl-D-aspartate receptor, VPA – valproate, WNT – wingless signaling pathway

Introduction

Apoptosis and programmed cell death play an important role in development of the organism, being engaged, for instance, in an early stage of central nervous system (CNS) formation, and fulfilling a crucial functional role. Apoptosis is a process of orderly cell removal through cell death. Apoptotic cell death is believed to be triggered by outer signals, whereas programmed cell death, a variety of apoptosis, is thought to be induced by intracellular-signals. Both these processes lead to elimination of pathologically changed and aging cells from the organism, and, in concert with proliferation, differentiation and maturation, contribute to the precise regulation of the number and type of cells. Apoptosis plays a fundamental role in preserving homeostasis within the body [1]. Cellular regulation of apoptosis is complex and incompletely understood. However, it is known that many mental disorders, neurodegenerative and tumor diseases are underlain by disrupted control of programmed cell death. It appears that external regulation of proapoptotic pathways would provide an opportunity for the development of new therapeutic strategies for mental disorders, principally affective ones, and injury-related CNS diseases [16]. For several years, evidences con-

cerning the neuroprotective effects of mood stabilizers has been gathered, and the antiapoptotic action of lithium and valproate (VPA) in particular has been recently reported [17].

Lithium and VPA are the most frequently used mood stabilizers. According to the definition by Rybakowski [64], mood stabilizing drugs (1) are effective in the therapy of mania or depression, (2) are effective in prophylaxis against manic and/or depressive episodes as demonstrated in trial of at least one year's duration and (3) do not worsen any aspects of the illnesses mentioned above. The efficiency of lithium salts was proven in the 1960s, however, their mechanism of action is still not entirely clear. It is known that lithium is an ion that easily penetrates across cell membranes, possessing an extra receptor target, stabilizes cell membranes of monoaminergic neurons and regulates water and electrolyte balance [6]. VPA (a derivative of valproic acid) is a mainstay in the treatment of different forms of epilepsy. As mentioned above, it has also been used in psychiatry, principally in the prophylaxis of bipolar disorder (BD) and as the second-line treatment in schizoaffective psychosis, when therapy with other drugs failed or when lithium carbonate or carbamazepine is contraindicated [24, 51, 63].

Experimental studied have demonstrated that mood stabilizers:

1) have protective action on hippocampal cells damaged by stress,
2) stimulate neurogenesis in rats,
3) decrease frequency of the *collapse-phase* in a sensory neuronal culture derived from dorsal root ganglia of rat fetuses,
4) inhibit apoptosis [67, 78].

At the molecular level, intracellular signal transduction *via* the inositol system, G-proteins, glycogen synthase 3β (GSK-3β), neuroprotective factor Bcl-2, protein kinase-C (PKC), histone deacetylase and proline oligopeptidase is a common target of these drugs [25].

In this article, we attempt to analyze the most recent reports of experimental studies on animal models showing the antiapoptotic properties of lithium and VPA. We focused principally on the influence of these drugs on intracellular signal transduction pathways during apoptosis and on pro- and antiapoptotic protein levels. Results of the newest molecular biology studies have indicated that mood stabilizers are inhibitors of apoptosis induced by stress factors [16, 26, 37, 56, 65, 80, 85]. Elucidation of the molecular mechanisms of the recently discovered antiapoptotic action of mood stabilizers is a potential key to their therapeutic efficacy in mental disorders and neurodegenerative diseases.

Antiapoptotic effects of lithium and VPA in *in vitro* studies

The antiapoptotic properties of lithium have become a focus of interest, and the number of experimental reports underlining the significance of this mechanism in inhibiting pathological-processes is on the rise. Jorda et al. [34] demonstrated the neuroprotective effects of lithium in primary cerebellar granule cell (CGC) cultures in which apoptosis was induced by colchicine exposure. Lithium supplementation (5 mM) decreased the number of neurons exhibiting features of apoptosis, like DNA fragmentation and chromatin condensation with a control group was, and these results were confirmed by immunofluorescence procedures. Antiapoptotic lithium effects were also demonstrated by Hennion et al. [29] in human neuroblastoma SH-SY5Y cell cultures. Cell damage was assessed by lactate dehydrogenase (LDH) release from the cytosol due to loss of cell membrane integrity. The study results clearly demonstrated that a strong LDH release induced by oubain (10 μM), a toxin blocking Na^+/K^+ pump, was statistically significantly inhibited by lithium.

It is believed that the molecular mechanisms of the therapeutic efficacy of lithium rely upon its interference with transmembrane exchange of cations such as Na^+ and K^+ which is disrupted in BD [30]. This mechanism is relevant to its antiapoptotic properties, which was confirmed by Mora et al. [52, 55]. They indicated that lithium efficiently suppressed apoptosis induced by low potassium concentration (5 mM) in CGC cultures. The extra- and intracellular concentration of potassium ions plays a crucial role in the regulation of switching within the cell between prosurvival and proapoptotic pathways. Due to the changes in K^+ concentration, lithium inhibits programmed cell death by (1) cell membrane stabilization in noradrenergic and dopaminergic neurons, (2) blockade of apoptosis-associated tyrosine kinase, and (3) activation of cyclic adenosine monophosphate (cAMP) and insulin growth factor [76]. Lithium also inhibits apop-

tosis induced by protein kinase B dephosphorylation arrest and by ceramide C2 (N-acetylsphingosine)-induced suppression of GSK-3β and protein phosphate (PP2A) [27]. Lithium can block the executor phase of apoptosis *via* activation of phospholipase c- γ and 3-phosphoinositol kinase (PI-3K), as was demonstrated by Chen et al. [11] using mouse glial cells. The authors suggested that lithium decreased the intracellular calcium pool and inhibited voltage-dependent calcium channel activation, which consequently prevented the cell from entering the apoptotic pathway. Zhong et al. [85] reported that lithium suppressed ethanol (400–1600 mg/dl)-induced apoptotic death of CGCs through the deactivation of caspases 3/9 and suppression of cleavage of the conservative PARP protein (ADP-ribose polymerase), whose main function consists of DNA double-strand break repair.

The antiapoptotic properties of lithium were confirmed by Beurel et al. [7] who indicated that this drug decreased sensitivity of cancer cells to apoptosis induced by chemotherapeutics. Lithium was demonstrated to significantly reduce camptotecin- and etoposide-induced apoptosis in several human intestinal cancer cell lines. Lithium chloride, as documented by Kappes et al. [37], inhibited proliferation of paraganglioma and pheochromocytoma cells due to blockade of GSK-3β, whose active form is considered to be a tumor growth-promoting factor. Results of the above-cited studies suggest that therapeutic use of these properties of lithium can become an adjuvant strategy in cancer therapy.

Almost all data indicate that lithium blocks the proapoptotic signal transmission cascade; however, Song et al. [73] observed that this drug can induce apoptosis as well. They noted that lithium at a 20 mM concentration significantly promoted apoptosis in Jurkat cells (cancer cell line derived from T lymphocytes) by stimulating the "death domain" containing FAS (cell surface receptor transduces apoptotic signals) receptors. As with lithium, despite some evidence of the antiapoptotic action for VPA found in *in vivo* studies, there are also contradictory data. Philips et al. [59] revealed that VPA at a 300 μM concentration induced apoptosis in the rat hepatoma-cell line FaO (hepatocellular carcinoma), as demonstrated by conventional markers of apoptosis (chromatin condensation, DNA fragmentation, increased caspase 11 expression, FAS receptor activation). These results suggested that the effects depend on the experimental models. Moreover, the hepatotoxicity of VPA observed in bipolar patients can acquire new meaning as it may be used in cancer treatment in the future. However, these interesting results obtained in cell culture have yet to be confirmed *in vivo.*

Antiapoptotic effects of lithium and VPA and their therapeutic efficacy in bipolar affective disorders

Mood disorders have been traditionally attributed to neurochemicals in the brain, but there is now some evidence that patients with bipolar affective disorders and major depression display morphometric changes suggestive of brain cell loss/or atrophy. Atrophy as a potentially reversible process may be an intermediate step leading to apoptosis. The preponderance of the data from the recent volumetric neuroimaging studies suggests an enlargement of the third and lateral ventricles, as well as reduced gray matter volumes in the orbital and medial prefrontal cortex, the ventral striatum and mesiotemporal cortex in patients with mood disorders [9]. Lucassen et al. [50] studied postmortem hippocampal tissues with respect to apoptosis. Using *in situ* DNA end-labeling they demonstrated a slighty increased rate of apoptosis in the dentate gyrus, CA1 and CA3 areas of the hippocampus in depressed and steroid-treated patients. In chronically stressed tree shrews, an animal model with high validity for depression, Czeh et al. [17] disorders are considered to be a novel class of neurodegenerative diseases. Apoptosis is suggested to contribute to neuronal loss in mood disorders, but at present, unequivocal empirical evidence of this idea has been lacking. Intense research conducted in the last decade has indicated that antidepressants from different classes, like reboxetine and tranylcypromine, increased levels of mRNA coding for the antiapoptotic protein Bcl-xl in the rat hippocampus. A lot of data suggest that (BD) arise from abnormalities in synaptic and neuronal plasticity. Mood stabilizing drugs that are effective in treating bipolar affective disorders have been shown to control synaptic plasticity and cellular resilience [16, 42, 66]. Lithium and VPA regulate a number of factors involved in the cell survival pathways, including: cAMP response element binding protein (CREB), brain-derived neurotrophic factor (BDNF), antiapoptotic protein (Bcl-2) and ex-

tracellular signal regulated protein (ERK)/mitogen-activated protein (MAP) kinases. They can up-regulate neurogenesis, the birth of progenitor cells, as well as their maturation and survival. It has been documented that therapy of manic-depressive patients with lithium exerts regenerative neurostructural (an increased gray matter volume in brains) and neurochemical effects (an increased level of the N-acetyl-aspartate – marker of neural viability and function) [45, 58]. The antiapoptotic and neuroprotective effects of VPA were corroborated by magnetic resonance studies in BD patients treated with this drug. The volume of the left cingulated gyrus of the hippocampus was increased in the patients, while its reduction is considered to be an endophenotype of this disease [9, 46, 64].

Several mechanisms are probably involved in the antiapoptotic action of mood stabilizers, but primarily the blockade of the phosphatidylinositol (PI) cascade. It is known that disruption of the PI cycle underlies pathophysiology of BD, whose symptoms are efficiently alleviated by lithium. Nuclear magnetic resonance studies of lithium-treated patients demonstrated an increased concentration of myoinositol (an important component of the PI secondary messenger system) in certain brain structures. Inhibition of myoinositol phosphate breakage leads to a decrease of calcium ion concentration, which is elevated in BD [45]. The latest clinical data have indicated that both mentioned drugs lower sodium-myo-inositol cotransporter mRNA expression in neutrophils of bipolar patients [79]. Accumulating evidence has clearly demonstrated that lithium and VPA at therapeutically relevant concentrations activate novel, secondary messenger cascades such as the ERK/MAPK survival pathway, which may mediate the antimanic effect of mood stabilizers [13, 30]. On the other hand, both of them reduce PKC activation that is up-regulated in BD patients and implicated in the pathophysiology of BD [51].

Antiapoptotic effects of lithium and VPA in *in vivo* studies. Their potential clinical significance in neurological diseases

Currently, all data concerning the antiapoptotic effects of lithium and VPA in Huntington's, Alzheimer's and Parkinson's diseases and ischemic stroke have come only from experimental investigation.

Studies on a model of Huntington's disease, which involves injection of a strong neurotoxin, quinolinic acid, into the striatum, revealed that lithium suppressed the executor phase of apoptosis [77]. Intracerebral administration of a neurotoxin, aluminum maleate, to rabbits elicited neurological deficits (hemiplegia, paralysis), while molecular changes in the hippocampus involved cytochrome c release, a decrease in the level of the antiapoptotic proteins (Bcl-2, and Bcl-xl) with a concomitant increase in the content of proapoptotic protein (Bax), caspase 3 activation and DNA fragmentation. Treatment of rabbits with lithium carbonate dissolved in drinking water restored the optimal level of regulatory proteins, i.e., predominance of Bcl-2 and Bcl-xl proteins paralleled with the down-regulation of Bax proteins in the CA1-4 pyramidal cell layer of the hippocampus and reduced DNA damage caused by aluminum maleate [26, 57, 65].

Clinical studies have revealed that radiotherapy of pathological changes within the skull cause long-term disturbances of cognitive functions, neurogenesis reduction and hippocampal neuron damage, particularly in children and the elderly. Yazlovitskaya et al. [81] presented interesting results demonstrating that lithium evoked the regression of post-radiation neurological deficits in mice and inhibited apoptosis of HT-22 mouse hippocampal neurons exposed to X-ray irradiation. Alleviation of the hippocampal irradiation-induced cognitive deficits in mice by lithium was investigated in the Morris water maze. Mice treated intraperitoneally with lithium (40 mg/kg) for 7 days before the irradiation found the escape platform twice as fast, which is a measure of drug efficacy. Parallel *in vitro* studies demonstrated that lithium (3 mmol/l) added to the irradiated hippocampal HT-2 cell cultures lessened some typical morphological features of apoptosis in neurons. Similar results were obtained during the histological examination of hippocampal slices from irradiated mice. LiCl-treated animals showed less pycnotic and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate biotin nick labeling (TUNEL) positive nuclei compared with a control group. Yazlovitskaya et al. have suggested that the radioprotective action of lithium is associated not only with GSK-3β inhibition due to lithium-induced PI-3K/AKT pathway stimulation, but also with a lowering of the proapoptotic tumor suppressor protein (p53) and Bax protein levels and elevating

Bcl-2 protein content. According to the authors, the antiapoptotic and neuroprotective effects of lithium could also be related to the regulation of antiapoptotic protein gene expression. Furthermore, cross-talk between lithium and neuronal apoptosis inhibitory protein (NAIP) is important in this discussion. NAIP is a representative of the IAP family (inhibitors of apoptosis protein in mammals inactivating caspase 3,7 and 9) and lithium – CDK-5, whose dysregulation, as suggested by the most recent studies, can be implicated in cell cycle dysfunction and the progression of neurodegeneration in Alzheimer's disease [4, 34, 52, 82].

There is a great hope that lithium can be used for the treatment of CNS injuries, intracranial cancers and neurodegenerative diseases. It is known that the fate of a cell under stress depends on many factors, like damage extent and type, and cell cycle phase. Ren et al. [62] demonstrated a neuroprotective effect of lithium injected at a dose of 1 mM after an ischemic episode in middle cerebral artery occlusion (MCAO) – the rat model of ischemic stroke. Neuroprotective effects against hypoxic-ischemic brain injury were observed by Kabakus et al. [35] in neonatal rats when given VPA. These effects were confirmed by molecular studies revealing the influence of lithium and VPA on the guardian heat shock proteins, (HSP)70-heat shock protein and (HSF)1, and DNA binding activity in post-ischemic regions. It was shown that lithium and VPA reduced ischemia and alleviated neurological deficits (as measured by motor performance) in the rat MCAO model. According to these authors, the neuroprotective effect of lithium resulted from strengthening of the HSP70 response to ischemic stress and a two-fold increase in DNA binding activity by HSF1 compared to the control group (ischemic but untreated with lithium and VPA), in which high HSP70 levels persisted for 24 h after ischemia and declined gradually within 3 and 7 days. In the lithium and VPA-treated groups, the level of these proteins at the same time points was much higher, which apparently promoted cell survival. Triggering of the prosurvival pathways by lithium and VPA can be a consequence of decreased GSK-3β activity, which inhibits HSF1 binding, or of the inhibition of p53 and Bax protein activity and/or diminished stimulation of N-methyl-D-aspartate (NMDA) receptors and nuclear factor-κB expression due to HSP70 hyperexpression, which is activated by ischemia and initiates the apoptotic cascade [17, 32, 58, 61, 62] (Fig. 1).

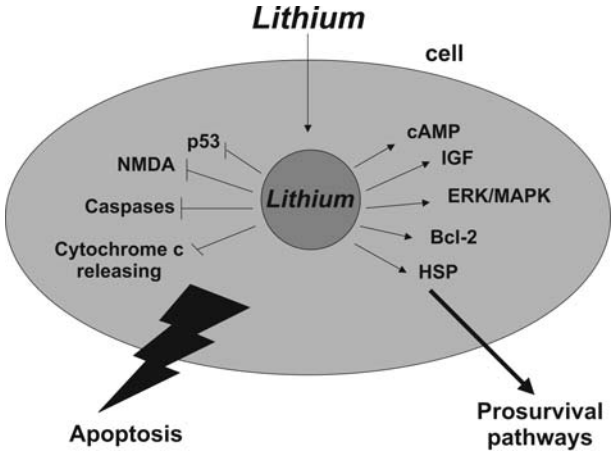

Fig. 1. Targets of antiapoptotic action of lithium associated with the modulation of intracellular protein activity. Bcl-2 – antiapoptotic proteins; cAMP – cyclic adenosine monophosphate, caspases – cysteine proteases that are one of the main executors of the apoptotic process, cytochrome c – mitochondrial intermembrane-space protein; ERK/MAP – mitogen activated protein kinase cascade, an essential component of the signal transduction mechanism; HSP – heat shock protein; IGF – insulin-like growth factor; NMDA receptor – N-methyl-D-aspartate – ionotropic receptor for glutamate; p53 – transcriptional factor that regulates the cell cycle, and has been described as the "guardian of the genome"

Due to its antiapoptotic activity, lithium and VPA presumably open new avenues in the therapy of mechanical CNS injuries. Su et al. [75] proved lithium salts to promote proliferation of progenitor nervous cells transplanted to damaged rat spinal cord, thereby facilitating the restitution of damaged neurons and reducing microglia and macrophage activity, thus minimizing the risk of graft rejection.

Karlovic et al. [38] showed that lithium increased the expression of p21 protein and surviving (belonging to IAP protein family) in human glioblastoma cells (A1235) and elicited cytostatic effects at 20 mmol/l on tumor cells. Lithium increased the expression of p21 protein (a cyclin-dependent protein kinase inhibitor) by influencing the p53 protein. Switching on pro- or antiapoptotic pathways involving DNA repair processes is regulated by the p53 protein, known as "the guardian of the genome". This protein induces G1 phase cell cycle arrest, thereby incapacitating the replication of damaged DNA, which constitutes a significant check point of the cell cycle. It is also known that the p53 protein is able to engage members of the Bcl-2 family in the regulation of cytochrome c release, which fulfils an undisputable role in apoptosis. Lithium's effect on the p53 protein is associated with the functional regulation of the HSP70 and HSP40

chaperones, which dissociate p53 aggregates under its hyperexpression. This effect confirms the antiapoptotic action of lithium [13, 16, 22, 43].

The most recent data on neurodegenerative diseases suggest that VPA and lithium suppress the phosphorylation of tau proteins and neurofibrillary tangle protein and block formation of β-amyloid aggregates, which are considered to be the main neurotoxic factor in Alzheimer's disease [25, 48]. These aggregates produce neurofibrillary tangles that block axonal transport in neurons, compose senile plaques and induce inflammatory processes. It has been proven that the beneficial therapeutic effects of lithium and VPA result from multidirectional protection consisting of: (1) DNA protection against oxidative damage, (2) blockage of tau protein hyperphosphorylation, (3) regulation of disturbed calcium homeostasis, (4) inhibition of caspase 12 involved in stress-induced apoptotic pathway endoplasmic reticulum (ER) (5) modulation of c-Jun N-terminal kinase and (ERK) [4, 12, 33, 41, 43]. As demonstrated by Shin et al. [70], lithium inhibited apoptosis in a mouse model of amyotrophic lateral sclerosis (ALS). The results unequivocally showed that LiCl treatment blocked apoptotic machinery through the suppression of FAS (cell surface receptor that transduces apoptotic signals) pathway activation (FAS is a ligand associated with tumor necrosis factor), diminution of reactive oxygen species levels and content of proapoptotic proteins, and reduced the motor dysfunctions characteristic of ALS [23, 70, 73, 74].

Results of recent experimental studies with lithium treatment in Parkinson's disease are promising. The antiapoptotic mechanism in this case prevents the nigrostriatal dopaminergic neuron decay, which is, at least partially, related to excitotoxic effect of glutamate on the cells. Parkinsonian-like symptoms in animals can be elicited by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injection, which is transformed into MPP^+ ions, increasing glutamatergic system activity [83]. Calcium overload in the cells and blockage of complex I of the respiratory chain leads to the activation of transcription factors c-Jun and p38, and the cell then enters apoptotic route. Chuang et al. [14] demonstrated that glutamate-induced cytotoxic effects could be inhibited by lithium, which suppresses NMDA receptors and stimulates (MAPK) and the Bcl-2.

It has been reported that VPA has the potential to benefit patients suffering from human immunodeficiency virus (HIV) with cognitive impairment. Dysfunctions in the CNS in HIV-dementia patients are associated with loss of neurons within certain regions of the brain and high levels of neuronal apoptosis. This state is the result of a production of numerous neurotoxic factors, like platelet activating factor, which may be inhibited by VPA, during the down-regulation of GSK-3β (activity of this enzyme may play an important role in the pathogenesis of HIV-associated dementia patients) [19].

However, the above recent experimental findings seem to be promising, but there is no clinical data that confirm lithium's therapeutic efficacy in the mentioned diseases.

Effect of lithium and VPA on intracellular signal transduction. Main targets of their antiapoptotic action

The above review of experimental data indicates that lithium salts and VPA have different targets through which they produce antiapoptotic effects by inhibiting the cell death cascade. The best known targets are PI and the wingless signaling pathway (WNT), PKC, GSK-3β and proteins of the HSP group.

The PI system is an important intracellular signal transduction pathway. Lithium was demonstrated to affect inositol-dependent processes using the genetically modified yeast *Dictiostellum discoideum*, in which defective cell aggregation was observed in an early developmental phase. It was shown that lithium increased inositol-1-phosphate synthase activity, which is the main inositol indicator *in vivo* [64, 78]. By inhibiting myoinositol phosphate breakage, lithium increases its concentration at the cost of free inositol, which is indispensable for PI resynthesis. In this way, lithium ions block the synthesis of secondary messengers diacylglycerol and 3-phosphate inositol (IP3) (Fig. 2). Blockade of the PI cascade results in: (1) decreased stimulation of muscarinic acetylcholine receptor and (2) inhibition of inositol monophosphatase. These two mechanisms lead to a lowering of calcium ion concentration [5, 21, 49, 60].

The influence of lithium on calcium level decrease by PI-mediated transmission blockade is involved in the antiapoptotic action of mood stabilizers. Calcium ions (Ca^{2+}) play a significant role in the activation of

apoptosis signaling (its concentration is higher in BD patients) [39]; therefore, in BD patients, it is important to restore Ca^{2+} level balance.

Long-standing lithium treatment also influences the PKC transduction pathway, which receives information from the PI system. Lithium and VPA inhibit PKC signaling, which may play an important role in the pathophysiology of BD, diminishing its level and activity, and reducing myristoylated alanine-rich C kinase substrate (MARCS) [28]. According to the latest data, the other drug – tamoxifen, which demonstrates antimanic properties, also significantly reduces the activity of PKC in rat brain [83].

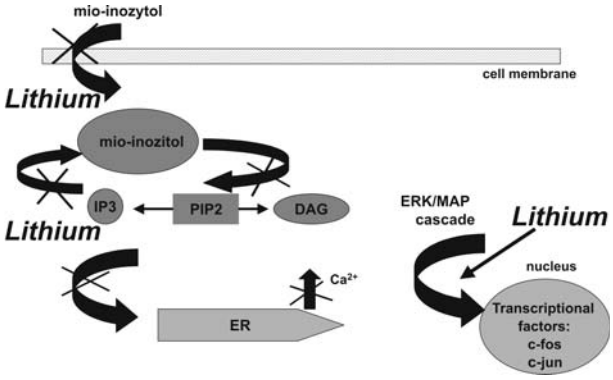

Fig. 2. Lithium ion as an inhibitor of inositol lipid intracellular transduction signaling. DAG – diacylglycerol, ER – endoplasmic reticulum, IP3 – 3-phosphate inositol – essential component of phosphoinozitol-pathway; PIP2 – phosphatidylinositol bisphosphate; substrate for cleavage with phospholipase C, products of this reaction are IP3 and DAG; activates calcium channels on ER; intracellular secondary messenger

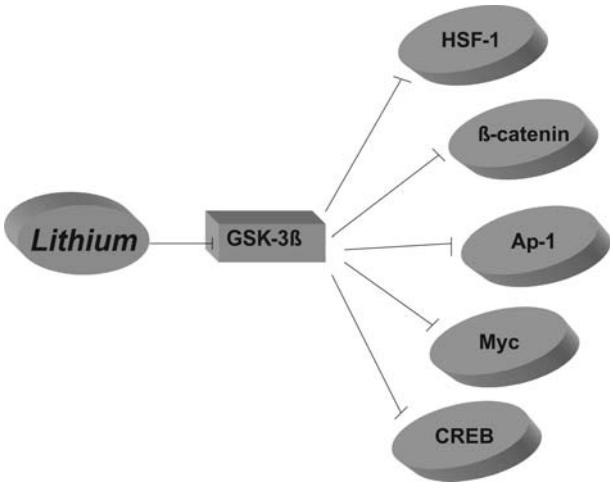

Fig. 3. Inhibition of proapoptotic signal transduction of glycogen synthase-3β by lithium. Ap-1 – multiprotein complex DNA binding; β-catenin – subunit of the cadherin protein complex, CREB – c-AMP response element binding which binds to DNA and increases or decreases transcription of certain genes; GSK-3β – glycogen synthase kinase; HSF – heat shock transcription factor protein; Myc – family of transcription factors

The next lithium target, GSK-3β, is a focal point of many signal transduction routes. GSK-3β affects 8 key transcription factors (e.g., AP1, LEF, Myc) and is an important target of mood stabilizing drugs. GSK-3β is a key element in the induction of pathways promoting programmed cell death [36, 54]. Therefore, the inhibition of this enzyme by lithium, which is its selective inhibitor, is to a large extent responsible for the antiapoptotic properties of the drug [15, 31, 33, 46, 68, 73] (Fig. 3). GSK-3β blocks prosurvival mechanisms implicating HSP and PI-3K/Akt, thereby limiting the cell's ability to cope with such insults as hypoxia, stress, or oxidative, osmotic and temperature disturbances. It is engaged in the pathomechanism of neurodegenerative diseases because it catalyzes tau protein phosphorylation, leading to their ubiquitination, thus increasing amyloid β-aggregation in Alzheimer's disease patients. Lithium's effect on GSK-3β was first observed in sensory neuron cultures derived from dorsal root ganglia of rat fetuses. Lithium (at a therapeutic dose of 0.8–1 mM) increased axonal branching proximal to the growth zone. The induction of proapoptotic pathways initiated by GSK-3β is efficiently suppressed by lithium at different stages. By inhibiting GSK-3β, lithium activates the β-catenin/WNT route [36, 44] (Fig. 4).

The WNT pathway is implicated in many physiological (growth and differentiation of tissues and organs) and pathological (carcinogenesis) processes, and components of this route have potential to treat many diseases. Many genes whose expression is induced by WNT play an important role in controlling apoptosis, the cell cycle and neoplastic transformation. The lithium-GSK-3β-β-catenin pathway regulation is crucial to functions fulfilled by β-catenin and its position in signal transmission. β-Catenin is the central molecule of WNT, which participates in different cellular processes like adhesion, differentiation, carcinogenesis, synaptic plasticity, nitric oxide synthase regulation (NOS2 – demonstrated *in vivo* and *in vitro*), and the WNT-dependent gene expression of c-Myc, cyclins D1, peroxisome proliferating activated receptor (PPAR) and cyclooxygenase (COX). Recently, it has been discovered that β-catenin activated transcription factor FOXO ("forkhead box proteins",

family of transciptional factors) governs responses under oxidative stress. When active WNT is absent, GSK-3β phosphorylates β-catenin at three positions: Ser33, Ser37, and Thr41. This destabilizes the protein and accelerates its proteosomal degradation. β-Catenin accumulation is an *in vivo* measure of its inhibition by GSK-3β [20, 44]. Ultimately, lithium activates the WNT signal transmission pathway that leads to the activation of many WNT-dependent routes. This action probably underlies the therapeutic effects of lithium salts in neuronal degeneration by stimulating survival pathways like PI3K/Akt signaling cascades [2]. Manipulating WNT signaling may play important role in BD patients.

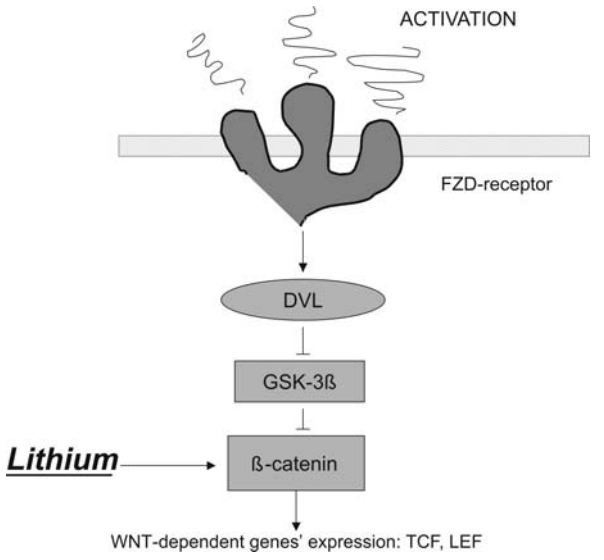

Fig. 4. Signal transmission within the WNT pathway and the effect of lithium on GSK-3β and β-catenin relation. β-Catenin – subunit of the cadherin protein complex, essential part of the WNT signaling pathway; DVL – protein is a critical component of WNT signaling pathway; FZD receptor – frizzled/WNT pathway receptor; WNT – wingless signaling pathway

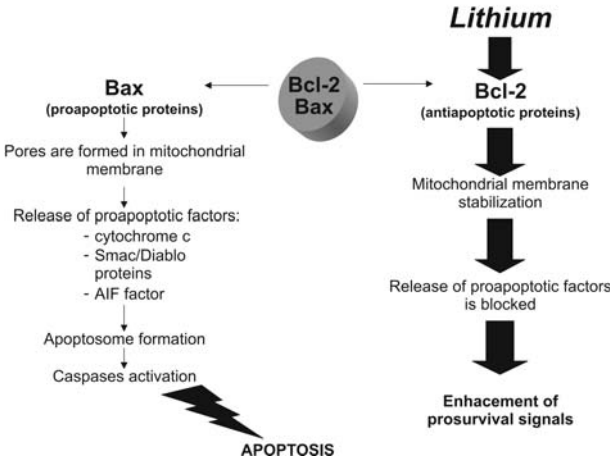

Fig. 5. Lithium implications in pro-survival pathway associated with the activation of antiapoptotic proteins of the Bcl-2 family. AIF factor – apoptotic inducing factor, major factor determining caspase-independent neuronal death; Apoptosome – large protein formed in the process of apoptosis from mitochondria in response to an intrinsic and an extrinsic death signaling; Bax – proapoptotic proteins; Bcl-2 – antiapoptotic proteins; cytochrome c – mitochondrial intermembrane-space protein; Smac/Diablo – protein (factor) that has been shown in response to apoptotic stimuli

Both of them are proapoptitic-GSK-3β inhibitors, decrease the phosphorylation of β-catenin (GSK-3β substrate) the nuclear translocation of β-catenin and increase the phosphorylation of Akt protein [72].

Lithium can stop the programmed cell death pathway by influencing Bcl-2 proteins that have pro- or antiapoptotic properties. These proteins, localized within the mitochondrial membrane, regulate membrane permeability, being able to influence the formation of pores or channels. Lithium increases the antiapoptotic protein level, thereby promoting the prosurvival pathway in the cell, which ultimately depends on an excess of apoptosis inhibitors over its promoters. In this way, lithium stabilizes the mitochondrial membrane and blocks the executor phase of apoptosis by disabling the release of proapoptotic molecules to the cytosol [8, 40, 53, 57] (Fig. 5).

VPA was shown by studies on different experimental models to produce antiapoptotic effects. It was shown to inhibit the transmission *via* the PI pathway by decreasing myoinositol transport and reducing the activity of PKC and MARCS, which are the enzymes indirectly linked to the PI route through the secondary messengers DAG and IP3. This mechanism may be implicated in the stimulation of neuronal growth observed *in vitro*. VPA amplifies prosurvival signals in the cell by the activation of antiapoptotic proteins of the Bcl-2 family, blockade of the proapoptotic caspase cascade and GSK-3β inhibition. VPA activates WNT genes, thereby increasing β-catenin synthesis, whereas catenin binds to cathedrins, presenilins and transcription factors, and influences synaptogenesis, proliferation and promotion of prosurvival signals [15, 52, 69] (Fig. 6).

According to pioneer studies, VPA combined with antiretroviral therapy (HAART) can be an efficient weapon in latent HIV infection management. This is due to its capacity to inhibit histone deacetylase (HDAC1), which plays a crucial role in preserving

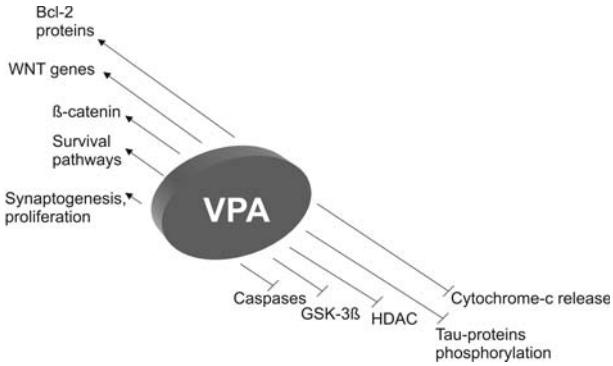

Fig. 6. Targets of antiapoptotic action of valproate (VPA). Bcl-2 – antiapoptotic protein; β-catenin – subunit of the cadherin protein complex; caspases – cysteine proteases that are one of the main executors of the apoptotic process; cytochrome c – mitochondrial intermembrane-space protein; GSK-3β – glycogen synthase kinase; HDAC – histone deacetylase; tau-proteins – microtubule-associated proteins which are involved (in phosphorylated form) in the pathogenesis of Alzheimer's disease and other tauopathies; WNT genes – WNT pathway genes like TCF and LEF

HIV in a latent state [71]. It is suggested that this is involved in the process of apoptosis [40].

Conclusions

Despite structural differences, lithium and VPA elicit the same clinical effect, namely, they stabilize mood. They show antiapoptotic actions at the cellular level, which is a significant component of their neuroprotective effect. Although the molecular mechanism of this action has not yet been elucidated in detail, it is known that the drugs influence many important messenger molecules [12, 15]. Data suggest that, due to the suppression of proapoptotic pathways and the amplification of prosurvival signals, lithium and VPA can become an efficient weapon in fending off neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's disease, Parkinson's disease, ALS), toxic factors and cognitive deficits resulting from CNS injuries [81]. Antiapoptotic effects also, at least partially, account for the therapeutic activity of both mentioned drugs in BD [3].

Results of *in vitro* studies on cell cultures suggest that PI pathway blockade, suppression of NMDA receptors, stimulation of ERK and MAPK and activation of the WNT route are the main targets of antiapoptotic action of lithium. On the other hand, VPA blocks the apoptotic cascade mostly *via* the inhibition of GSK-3β, PKC and MARCS, by lowering myoinositol transport and increasing β-catenin activity, which is the central biomolecule in the WNT pathway. Lithium and VPA presumably decrease SMIT mRNA expression, as demonstrated on neutrophils of bipolar patients using RT-PCR [79]. According to western blot analysis in an animal model of cerebral ischemia, these drugs increase the level of regulatory proteins of the HSP family, which result in a reduction of ischemia-induced neurological deficits, including cognitive disorders. At the molecular level, this action provokes blockade of transit of apoptosis-initiating factors from the mitochondria to the cytosol (including cytochrome c), and it elevates HSF binding to DNA, thereby switching the cell to prosurvival routes. Lithium and valproic acid equally inhibit tau protein hyperphosphorylation, which can be relevant to Alzheimer's disease therapy [62].

Despite the preponderance of experimental reports authenticating the antiapoptotic action of lithium and valproic acid, there are studies demonstrating their apoptosis-promoting effect. These data suggest that the ultimate effect depends on the drug dose and experimental model. VPA was shown to induce apoptosis in the rat hepatoma cell line FaO, whereas lithium activated apoptosis related to FAS receptors in Jurkat cells [57, 73, 84].

The results obtained thus far appear to be interesting from a therapeutic standpoint. A majority of the studies were conducted with lithium in *in vitro* models. Therefore, further *in vivo* studies and clinical trials are needed in order to better understand the effect of mood stabilizers on apoptosis, which may facilitate the therapeutic use of these drugs.

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