Pharmacological Reports xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

The effect of lithium on hematopoietic, mesenchymal and neural stem cells

Ewa Ferensztajn-Rochowiak, Janusz K. Rybakowski *

Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznań, Poland

ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form 14 September 2015
Accepted 14 September 2015
Available online xxx

Keywords:
Lithium
Hematopoietic stem cells
Mesenchymal stem cells
Neural stem cells
Glycogen synthase kinase-3

ABSTRACT

Lithium has been used in modern psychiatry for more than 65 years, constituting a cornerstone for the long-term treatment of bipolar disorder. A number of biological properties of lithium have been discovered, including its hematological, antiviral and neuroprotective effects. In this article, a systematic review of the effect of lithium on hematopoietic, mesenchymal and neural stem cells is presented. The beneficial effects of lithium on the level of hematopoietic stem cells (HSC) and growth factors have been reported since 1970s. Lithium improves homing of stem cells, the ability to form colonies and HSC self-renewal. Lithium also exerts a favorable influence on the proliferation and maintenance of mesenchymal stem cells (MSC). Studies on the effect of lithium on neurogenesis have indicated an increased proliferation of progenitor cells in the dentate gyrus of the hippocampus and enhanced mitotic activity of Schwann cells. This may be connected with the neuroprotective and neurotrophic effects of lithium, reflected in an improvement in synaptic plasticity promoting cell survival and inhibiting apoptosis. In clinical studies, lithium treatment increases cerebral gray matter, mainly in the frontal lobes, hippocampus and amygdala. Recent findings also suggest that lithium may reduce the risk of dementia and exert a beneficial effect in neurodegenerative diseases. The most important mediators and signaling pathways of lithium action are the glycogen synthase kinase-3 and Wnt/β-catenin pathways. Recently, to study of bipolar disorder pathogenesis and the mechanism of lithium action, the induced pluripotent stem cells (iPSC) obtained from bipolar patients have been used.

Contents

Abbreviations: Akt, protein kinase B; Bcl-2, B-cell lymphoma; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BFU-E, burst forming unit-erythroid; BrdU, bromodeoxyuridine; cAMP, cyclic adenosine monophosphate; CFU-Baso, colony forming unit-basophil; CFU-blast, colony forming unit-blast; CFU-E, colony forming unit-erythroid; CFU-Eo, colony forming unit-eosinophil; CFU-G, colony forming unit-granulocyte; CFU-GEMM, colony forming unit-granulocyte, erythrocyte, macrophage, megakaryocyte; CFU-GM, colony forming unit-granulocyte, monocyte; CFU-L, colony forming unit-lymphocyte; CFU-M, colony forming unit-monocyte; CFU-Meg, colony forming unit-megakariocyte; CREB, cAMP response element-binding protein; CSA, colony stimulating activity; CSF, colony stimulating factor; CXC4, chemokine receptor 4; DCX, doublecortin; G-CSF, granulocyte colony-stimulating factor; GFAP, glial fibrillary acidic protein; GM-CFS, granulocyte-macrophage colony-stimulating factor; GMP, granulocyte and monocyte progenitors; GSK-3, glycogen synthase kinase-3; HIF-1, hypoxia-inducible factor-1; HPC, haematopoietic progenitor cells; HSC, hematopoietic stem cells; IMP, inositol monophosphatase; iNLC, induced neuronal-like cells; IP3, inositol triphosphate; iPSC, induced pluripotent stem cells; LiCl, lithium chloride; LRP5, low density lipoprotein receptor related protein 5; Meg-CSF, megakariocyte colony-stimulating factor; MMP-9, matrix metaloproteinase-9; MSC, mesenchymal stem cells; mTOR, mammalian target of rapamycin; NeuN, neuronal nuclear protein; NSC, neural stem cells; Oct4, octamer-binding transcription factor 4; PBMCs, peripheral blood mononuclear cells; PFC, prefrontal cortex; PI, phosphatidylinositide; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PKC, protein kinase C; PTEN, phosphatase and tensin homolog deleted; SC, stem cells; SDF-1, stromal cell-derived factor 1; SSEA4, stage-specific embryonic antigen 4; TBARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor alpha; VPA, valproic acid; VSELs, very small embryonic-like stem cells; WBC, white blood cells.

* Corresponding author.
E-mail address: janusz.rybakowski@gmail.com (J.K. Rybakowski).

http://dx.doi.org/10.1016/j.pharep.2015.09.005
1734-1140/

Introduction

The introduction of lithium to modern psychiatric treatment began in 1949, when the Australian psychiatrist, John Cade, described the therapeutic properties of this ion in manic patients [1]. Over the past 65 years of lithium's presence in psychiatry, its unique properties, including the antiviral, immunomodulatory and neuroprotective effects, have been discovered. As early as the year after Cade's paper, Radomski et al. [2] noted an increase in white blood cells in patients treated with lithium, showing a distinct effect of this ion on the hematopoietic system. In the 1970s and 1980s, the first reports of the beneficial effects of lithium on hematopoietic stem cells (HSC) and hematopoietic growth factors appeared. In the past two decades, with the development of stem cell knowledge, the effects of lithium on mesenchymal stem cells (MSC) and neural stem cells (NSC) have been demonstrated. In this paper, a systematic review of the effect of lithium on hematopoietic, mesenchymal and neural stem cells will be presented. The PubMed/MEDLINE and Cochrane Library databases were searched through June 1, 2015, using the keywords "lithium" and "stem cells". The related articles studying effects of lithium on hematological system and on neurogenesis were also included and discussed.

Stem cells (SC) are characterized by their unique ability of self-renewal and differentiation into progenitors and tissue-committed cell populations from all three germ layers, mesoderm, ectoderm and endoderm [3]. The developmental continuum comprises totipotent, pluripotent, multipotent SC and cells committed to one developmental lineage (unipotent). Multipotent stem cells include hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and neural stem cells (NSC).

Hematopoiesis has four stages. It begins with bone marrow-derived hematopietic stem cells (HSC). They produce CFU-blast (colony forming unit-blast), CFU-GEMM (colony forming unit-granulocyte, erythrocyte, macrophage, megakaryocyte) generating myeloid lineage and CFU-L (colony forming unit-lymphocyte) for lymphoid lineage. Subsequently, precursor cells committed for granulocyte-macrophage lineage – CFU-GM (colony forming unit-granulocyte, monocyte), CFU-G (colony forming unit-granulocyte), CFU-M (colony forming unit-monocyte), CFU-Eo (colony forming unit-eosinophil), CFU-Baso (colony forming unit-basophil); for erythroid lineage – BFU-E (burst forming unit-erythroid), CFU-E (colony forming unit-erythroid); for megakariocyte lineage – CFU-Meg (colony forming unit-megakariocyte) are formed. Finally, morphologically differentiated cells: granulocytes, monocytes, erythrocytes, platelets and lymphocytes develop, accompanied with overall effect of hematopoietic growth factors, i.e. CSF (colony stimulating factor) [4].

Neural stem cells can differentiate into neurons, astrocytes and oligodendrocytes. The classical scheme presents a development of neural stem cells and neuroprogenitors, which differentiate into immature and mature neurons as well as glioblasts which produce astrocytes and oligodendrocytes. In the new scheme, radial glia-like cells develop from neuroepithelial stem cells through ventral and dorsal stem cells, which under certain conditions can produce progenitor cells and further, neurons and astrocytes. The neurogenesis in adult brain includes two main streams, which involve neuroprogenitor cells and their neural precursors, in subventricular zone, and cells in the subgranular layer of the hippocampus. Some researchers propose a concept of neural stem cells spectrum and the term "neural precursors" for neural stem cells and neuroprogenitors, with underscoring the role of cellular microenvironment for further differentiation [6].

The effect of lithium on hematopoietic stem cells and growth factors

Since 1950 when the first paper was published on lithium-induced leukocytosis in bipolar patients [2], this effect has been continuously reported [7–9]. The observation of increased production of some blood cells by lithium inspired studies into its effect on the initial stages of hematopoiesis. It has been found that lithium induces marrow granulopoiesis, influencing hematopoietic stem cells (HSC). Lithium influences stem cells (SC) directly, by stimulating pluripotent stem cell (PSC) proliferation, and indirectly, by increasing production of granulocyte colony-stimulating factor (G-CSF) and other growth factors. Hammond and Dale [10] demonstrated that administration of lithium to dogs with cyclic neutropenia eliminated abnormalities in neutrophils, as well as in platelets, reticulocytes and monocytes, indicating the effect of lithium on the HSC level. Levitt and Quesenberry [11] found that lithium primarily stimulates pluripotential stem cells and the progenitor cells for granulocytes and monocytes (GMP).

In the 1980s, an effect of lithium on pluripotent cells and myeloid, erythroid and megakariocyte progenitor cells was also observed. In an animal model, increases in CFUs, bone marrow cellularity and peripheral white blood cells (WBC) were demonstrated [12]. Joyce found, in an animal model, that lithium increases colony stimulating activity (CSA), together with neutrophil and platelet counts [13]. These effects were preceded by an elevation in the marrow production of neutrophils and concentrations of colony forming units for granulocyte and monocyte (CFU-GM), megakaryocyte (CFU-M) and erythrocyte (BFU-E and CFU-E) progenitor cells. Ballin et al. [14] investigated whether lithium increased the number of CD34+ HSCs in eight adult patients with bipolar disorder (BD). After 3–4 weeks, there was a peak in the CD34+ cell number and neutrophil count by an average of 88%. Moreover, a significant correlation between an increase in neutrophils and the number of CD34+ cells has been demonstrated. Huang et al. [15] have shown that glycogen synthase kinase-3 (GSK-3) inhibitors, including lithium, improve the homing process, the ability to form colonies and HSC self-renewal, during implantation into the donor organism. Walasek et al. [16] have demonstrated that a combination of lithium and valproic acid (VPA) has the strongest effect on the progenitor HSC, rather than either of the compounds alone. A synergistic effect on the enhancement of the self-renewal processes, the inhibition of differentiation, shorter time of platelet and erythrocyte recovery, and these impacts on the expression of 360 genes was observed.

The second important effect of lithium is to stimulate the production of hematopoietic growth factors. In healthy persons

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005

lithium administration results in an increased release of G-CSF and increased bone marrow neutrophil production *in vitro* [17]. Elevated G-CSF levels in the urine [18] and enhanced production of G-CSF by peripheral blood mononuclear cells (PBMCs) [19] were observed. Gamba-Vitalo et al. [20] showed indirect effect of lithium on megakariocytopoiesis by influencing Meg-CSF and a direct effect on CFU-Meg. In the presence of lithium, enhanced sensitivity of CFU-Meg to stimulation with growth factors, expressed as an increase in a concentration of 200% was observed.

The effect of lithium on mesenchymal stem cells

In the last few years, a number of studies have been conducted on the effect of lithium on mesenchymal stem cells (MSC). These cells can differentiate into chondrocytes, osteoblasts or adipocytes. Eslaminejad et al. [21] studied human MSCs cultures induced by TGF-β (transforming growth factor-β) in order to differentiate toward chondrocytes. The addition of glycogen synthase kinase-3 (GSK-3) inhibitors – lithium chloride (LiCl) in a concentration of 5 mmol/l, and the SB216763 molecule, caused an up-regulation of specific cartilage genes expression and an increase in glycosaminoglycan synthesis. However, Kapadia et al. [22] studying the influence of LiCl, at a concentration of 15 mmol/l, on endochondral ossification of rat embryonic cells noted an inhibition of cell differentiation into the chondrocytes and osteoblasts of the perichondrium, expressed by a decline in the expression of the cartilage proteoglycans. Similar decreases were noted by Kawata et al. [23] after activation of the Wnt/β-catenin pathway by SB216763 molecule in human chondrocytic cells, but without incubation with TGF-β. de Boer et al. [24] found that low activity of the Wnt pathway causes a proliferation of uncommitted human MSC. On the other hand, increased activation of this pathway results in an inhibition of differentiation toward adipocytes and the initiation of osteogenesis. These authors conclude that lithium maintains the pluripotency of MSC, inhibits expression of bone formation and of chondrogenesis markers, and partially blocks the MSC mineralization processes [25].

Clément-Lacroix et al. [26], after 4 weeks of lithium therapy in low density lipoprotein receptor related protein 5 (LRP5) gene knockout mice with reduced bone mass, found restored bone metabolism and normal bone mass. They proposed that lithium could be an adjunctive drug for the treatment of osteopenic disorders, by enhancing the Wnt/β-catenin signaling pathway and differentiation into bone tissue. Chen et al. [27] reported that the use of lithium resulted in the acceleration of fracture healing in mice. This process was observed only when lithium was administered at a later stage of repair, after MSC differentiation into osteoblasts. Edwards et al. [28] observed that treatment with lithium chloride results in the activation of differentiation into osteoblasts and prevents the development of multiple myeloma in an animal model. Epidemiological studies in humans have demonstrated that lithium treatment is associated with a reduced risk of fracture [29], which indicates the anabolic properties of lithium within bone [30]. Zamani et al. [31] conducted a densitometric study in 75 patients (mean age 37 ± 10 years) treated prophylactically with lithium for a minimum of one year, resulting in greater bone density, compared with the control group. The authors suggest that lithium therapy reduces bone turnover, allowing maintenance of or increase in bone mass.

Satija et al. [32] reported the suppression of cell proliferation and an increase in alkaline phosphatase activity of human MSC during lithium therapy, as well as a decreased expression of genes associated with adipocytes and lipid synthesis, and the up-regulation of genes involved in mineralization. The authors suggest that the lithium effect on the differentiation of MSC is dependent on the concentration and duration of administration. Lithium concentrations less than 5 mmol/l promote, while higher inhibit, the proliferation of MSC. They conclude that lithium affects the MSC directly and indirectly, at the transcription and posttranscriptional level, and genes which affect osteogenesis play a role in the later stages of osteoblast differentiation.

Tsai et al. [33] showed an increased ability to migration and homing of MSC during lithium, and/or VPA, therapy in an animal model of stroke, which was reflected by functional improvement, reduction of the ischemic area and enhancement of angiogenesis. These effects were mediated by increased expression of the CXC chemokine receptor 4 (CXCR4), and matrix metalloproteinase-9 (MMP-9) for VPA and lithium, respectively. The authors report that both the interactions of stromal cell-derived factor 1 (SDF-1)/CXCR4 and MMP-9 are essential for the homing ability of stem cells.

The effect of lithium on neural stem cells

The effect of lithium on neurogenesis has been demonstrated in many studies. In 1987, Yoshino and DeVries found enhanced mitotic activity of Schwann cells after the addition of lithium [34]. Kim et al. [35], in their *in vitro* and *in vivo* studies, found an increased number of mature neuronal cells labeled with nuclear protein NeuN (neuronal nuclei), indicating the intensity of the processes of neuronal differentiation of progenitor cells after lithium treatment. Son et al. [36], conducting injections of bromodeoxyuridine (BrdU), demonstrated a significant 54% and 40% increase in the number of BrdU-positive cells in the rat dentate gyrus, after 12 h and 28 days, respectively, after completing chronic 28-day lithium treatment protocol. Chen et al. [37] and Li et al. [38] described an enhanced proliferation of progenitor cells in the hippocampus (BrdU-labeled). In the first study [37], lithium administration resulted in a 25% increase in the number of BrdU-labeled cells in the dentate gyrus of the hippocampus and approximately two-thirds of the BrdU-positive cells were double-labeled with the neuronal marker NeuN. The authors suggest that chronic lithium treatment increases also the number of non-neuronal cells, including progenitor cells and glia.

In an animal model of ischemic stroke, lithium administration immediately, and for the next 7 days after a stroke, caused a reduction in the loss of neural tissue by 69% in the 7th week of the study. The authors suggest that lithium can provide long-term protection from the consequences of stroke by enhancing the proliferation and survival of neural progenitor cells, and inhibiting inflammatory processes [38]. Kang et al. [39] showed that lithium pretreatment reduces brain injury after intracerebral hemorrhage in rats, as measured by diminished hemispheric swelling and atrophy and reduced cell death. Huo et al. [40] assessed the effect of lithium on survival and differentiation of hippocampal cells of mice exposed to radiation. There was a 24% increase in the number of BrdU-labeled cells six hours after irradiation and a 59% increase in the 7th week of the study, indicating a long-term effect. Lithium also reduced the apoptosis of progenitor cells in the granular layer of the hippocampus. However, O'Leary et al. [41] observed that chronic lithium treatment increases cell proliferation in the ventral hippocampus only under stress conditions, and that this process is associated with a reduction in the survival of newly born cells.

Recently, Kara et al. [42] investigated the effects of lithium on neurogenesis in the subgranular zone of the dentate gyrus in adult mice [42]. They studied various stages of the development of progenitor cells (types I, IIa, IIb, and III), examining specific markers such as Nestin, glial fibrillary acidic protein (GFAP), doublecortin (DCX), and NeuN. They found that lithium treatment increases cell proliferation in the early developmental stages (type I), does not affect the neuroblasts (type IIb), nor the number of immature neurons (type III), and reduces the process of morphological maturation. The authors conclude that lithium

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005

targets the initial stages of progenitor development by enhancing turnover of neural progenitor cells. However, these processes are not translated into an increase in the number of newly born neurons. The effect of lithium is similar to electroconvulsive-therapy, targeting type I cells [43], but distinct from antidepressant drugs which target type IIa cells [44].

Hill et al. [45] evaluated the effect of lithium and VPA on the expression of genes related to the differentiation of nerve cells. Lithium did not change the proportion of cells expressing markers of stem cells, such as octamer-binding transcription factor (Oct4), stage-specific embryonic antigen 4 (SSEA4), neurons (neurofilament M), astrocytes (GFAP) or cell cycle phases, but it produced a 1.4-fold increase in total cell number. On the other hand, VPA caused upregulation of markers such as Oct4, SSEA, neurofilament M, and GFAP, a decrease of cells in the G2/M cell cycle phase and a decrease in total cell number.

It should be emphasized that reports of the results of research on neural stem cells may be dependent on methodological differences, the assessment of various markers, different results of *in vivo* and *in vitro* studies and different regimes of lithium administration. For example, Hasgekar et al. [46] demonstrated lithium-induced growth inhibition of animal neural cell lineage and Misiuta et al. [47] observed different effects of lithium on human neuronal stem cells (NSC) and precursor cell lineage.

A favorable effect of lithium on neural stem cells and on neurogenesis may be connected with neuroprotective properties of the lithium. On the clinical level, this may be reflected in an increase in cerebral gray matter, mostly that of the frontal lobes, hippocampus and amygdala in lithium-treated bipolar patients. Yucel et al. [48] found bilateral increases in volume of the hippocampus of bipolar patients over 8-weeks and 4-years of treatment with lithium. Bearden et al. [49] found significantly larger hippocampal volumes in lithium-treated bipolar patients compared with healthy controls and non-medicated patients. Lyoo et al. [50] found a lithium-induced gray matter volume increase through 16 weeks of treatment, compared with an absence of effect in patients treated with VPA or in healthy controls. Hallahan et al. [51] analyzed 321 bipolar patients and 442 healthy individuals and found that patients taking lithium displayed significantly increased hippocampal and amygdala volumes compared to patients not taking lithium and a control group. The longitudinal study of Selek et al. [52] indicated significant enlargement in the left prefrontal cortex (PFC) and left dorsolateral PFC in bipolar I patients who responded to 4-week lithium treatment. Recently, Hajek et al. [53] found increased hippocampal volume in bipolar patients receiving lithium, compared to patients receiving other mood-stabilizing drugs independent of a long-term lithium response.

The mechanisms whereby lithium increases synaptic plasticity, promotes cell survival and inhibits apoptosis involve several systems. These include the brain-derived neurotrophic factor (BDNF), GSK-3, cyclic adenosine phosphatase (cAMP), cAMP response element-binding protein (CREB), the phosphatidylinositide (PI) cascade, protein kinase C (PKC) and B-cell lymphoma-2 (bcl-2) [54]. All of these factors are involved in the maintenance of stem cell viability. In lithium-treated bipolar patients, a correlation was found between left amygdala volume and serum BDNF levels [55] and between increased gray matter volume of the right frontal lobe and GSK-3β genotypes [56]. Allaqui et al. [57] involved SH-SY5Y cells derived from a human neuroblastoma and cultured in the presence of 0.5 mM lithium for 25 weeks, found that they displayed higher cell growth rates and lower basal levels of lipid peroxidation measured as thiobarbituric acid reactive substances (TBARS), and concluded that chronic lithium treatment could improve neurogenesis and decrease the vulnerability of neuronal cells to oxidative stress.

A number of recent clinical and experimental studies have pointed to a beneficial effect of lithium in neurodegenerative disorders. Lithium may reduce the risk of dementia [58,59] and prevent cognitive loss in Alzeimer's disease [60]. This may be due to inhibition of GSK-3, a key enzyme related to amyloid precursor protein processing and the phosphorylation of the tau protein. In an animal model of Alzheimer's disease, Sofola-Adesakin et al. [61] described lithium-induced suppression of amyloid pathology by reducing protein synthesis and the level of amyloid-β42. Senatorov et al. [62] have shown a neuroprotective effect of lithium in an animal model of Huntington disease, by stimulating the proliferation of neural progenitor cells and astroglial cells.

Recently, Dong et al. [63] studied the potential promotion of lithium on MSC proliferation and neural differentiation *in vitro* and after transplantation into the ventral horn of rat spinal cord *in vivo.* They demonstrated lithium's ability to promote proliferation of MSCs, verified by increased BrdU incorporation. After transplantation of MSCs into the rat spinal cord, lithium treatment enhanced cell survival and neural differentiation. They conclude that lithium could be a potential drug to augment the therapeutic efficiency of MSCs transplantation therapy in central nervous system disorders.

Molecular mechanisms of lithium action

The most important systems and signaling pathways mediating the action of lithium on stem cells are glycogen synthase kinase 3 (GSK-3) and the Wnt/β-catenin pathway. Additional mechanisms of lithium action involve the cAMP, protein kinase B, phosphatidylinositol 3-kinase (PI3 K) and inositol monophosphatase (IMP) levels. The above mechanisms of action have already been mentioned in the previous sections.

A key mechanism of lithium action is its ability to block glycogen synthase kinase-3 (GSK-3), which has two isoforms, GSK-3α and GSK-3β, encoded by different genes, but having 98% homology. GSK-3 phosphorylates a number of proteins which, in most cases, leads to their inactivation. Lithium, in a concentration of 2 mmol/l, inhibits GSK-3 directly, while at concentration of 0.8 mmol/l it acts indirectly by leading to increased phosphorylation of GSK-3 through protein kinase B (PKB/Akt). Neutrophilia due to inhibition of GSK-3 by lithium is triggered by a shift in the balance of the basic processes of hematopoiesis. A reduction in GSK-3 activity abolishes phosphorylation and thus enhances the activity of the transcription factor HIF-1 (hypoxia-inducible factor-1). Bone marrow trophic niches attract and retain HSC indirectly by HIF-1, which stimulates transcription of stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4. The concentration gradient of SDF-1 forms a signal for the HSC homing to the bone marrow niche [64]. The effect of lithium on haematopoiesis takes place through the interaction of GSK-3 and HIF-1, where the inhibition of GSK-3 indirectly increases the gradient of SDF-1 toward the hypoxic bone marrow trophic niche, where the HSC can evolve. Increased activity of bone marrow trophic niche and the homing process are reflected as peripheral neutrophilia, thrombophilia and an increased number of CD34+ cells [65].

Huang et al. [66] suggest that GSK-3 may play a pivotal role in the homeostasis of HSC in mice. Lithium, by blocking GSK-3, may regulate key elements of this process, affecting a number of important signaling pathways such as Wnt and PI3 K/phosphatase and tensin homolog deleted (PTEN)/Akt [67,68]. Transplantation studies in mice have shown that the administration of GSK-3 inhibitors increases the number of hematopoietic stem cells (HSC) and haematopoietic progenitor cells (HPC) [67,69]. In addition, impairment of GSK-3 (by inhibitors or a knock-out variant of the gene) will enable embryonic stem cells to remain pluripotent [70] and to express markers of pluripotency [71].

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005

The Wnt signaling pathway plays a central role in the self-renewal of various stem cell populations. Researchers have found that the knockout of GSK-3 gene increased the number of HSC, similar to lithium or other GSK-3 inhibitors, and that the functional endogenous β-catenin is necessary in this process. On the other hand, longitudinal studies on stem cell functioning showed that the number of HSC that lacked GSK-3 gradually decreased, indicating the role of GSK-3 in maintaining HSC self-renewal capacity. Huang et al. [66] suggest the dual role of GSK-3 in homeostasis, ensuring a balance between self-renewal and differentiation of HSC. A blockade of GSK-3 activates two different signal pathways – mTOR (mammalian target of rapamycin) and Wnt, causing opposite effects. A blockade of GSK-3, involving PI3 K, PTEN and Tsc, activates the mTOR pathway and promotes differentiation processes. On the other hand, inhibition of GSK-3 through the Wnt/β-catenin pathway, results in the activation of genes involved in the proliferation and self-renewal of the progenitor cells.

It is assumed that the Wnt/β signaling plays a central role in the MSC activity, whereas inhibition of GSK-3 results in pathway activation by stabilizing β-catenin. A potentially significant association exists between lithium induced increased length of primary cilia [72], and their effects on Wnt signaling, and enhanced cell reactivity during chondrogenesis. Also, the Wnt/β-catenin signaling pathway is essential for the MSC differentiation processes in bone formation.

A significant effect of lithium on hematopoiesis may be exerted through inositol monophosphatase (IMP), which indirectly controls the signaling pathway of inositol triphosphate (IP3). However, Wexler et al. [73] found that stimulation of progenitor cell proliferation in the hippocampus is independent of IMP, but dependent on both Wnt signaling and GSK-3 inhibition. GSK-3 inhibitors mimic the effect of lithium on the HSC and progenitor cells, and a decrease in GSK-3α and GSK-3β activity also affects more differentiated cells of the myeloid lineage [69,74,75]. It is possible that a lithium induced increase in the number of HSC through a β-catenin dependent pathway is compensated by activation of the mTOR pathway and an increase in differentiation, as reflected by rises in the number of mature blood cells, especially those of myeloid lineage. In a later study, Huang et al. [15] demonstrated that the most favorable factor for the long-term survival of HSC is the use of lithium, together with inhibitors of the mTOR pathway.

Modulation of granulopoiesis and megakaryocytopoiesis by lithium may also be related to the transport of cations across the cell membrane [76]. Intensification of these processes is observed in the presence of sodium, but not of potassium or calcium ionophores. The presence of ouabain – an inhibitor of Na-K ATPase, causes irreversible inhibition of stem cell potentiation (CFU-GM). Sodium transport inhibitors reduce the ability of lithium to increase CFU-GM. Calcium active transport was also found to have an inhibitory effect on lithium-induced granulopoiesis. Yoshino and DeVries [34] found, in their *in vitro* studies, that the addition of lithium increases the mitogenic activity of Schwann cells in the presence of calcium channel blockers – nifedipine or manganese cations (Mn^{2+}).

Lithium also influences the activity of the hematopoietic system by modulation of the immune system, including changes in the concentrations and activity of some interleukins [77]. Kleinerman et al. [78] report that one of the mechanisms of lithium action causing granulocytosis may be an enhanced TNF-α production and its secretion by monocytes. Gallicchio et al. [79] reported that the increase in the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) by lithium can be achieved by reducing the inhibitory effect of prostaglandins on GM-CSF. Despite the administration of antibodies against factor CSF-1, Doukas et al. [80] observed lithium induced stimulation of granulocyte progenitor cells, which suggests an additional indirect mechanism of lithium action.

Pluripotent stem cells, bipolar disorder and lithium

Recently, the induced pluripotent stem cells (iPSC) obtained from bipolar patients have been used to study the pathogenesis of bipolar disorder and the mechanism of lithium action. iPSC have a tri-lineage differentiation capacity similar to that of embryonic stem cells (ESC) and can be obtained from somatic cells and the reprogramming protocols involving vectors carrying genes of pluripotency.

In their first research on cell lines derived from BD patients, Chen et al. [81] obtained dermal fibroblasts from three BD patients and three controls and transduced them into iPSC with retroviral constructs and followed 8 weeks of neuronal differentiation. They found that BD patient-derived neurons are characterized by increased expression of transcripts for membrane bound receptors and ion channels, particularly those involved in calcium signaling, as well as in the expression of genes involved in the differentiation of ventral regions and GABAergic interneuron differentiation, significantly different from neurons obtained from controls. Lithium pretreatment (with 1 mM of LiCl 24-h before testing) altered signaling in BD neurons, significantly decreasing calcium transient and wave amplitude, compared with control neurons. The authors suggest that this effect of lithium may be due to inducing the Wnt pathway.

In another report published by Wang et al. [82] a cell adhesion phenotype of induced neuronal-like cells (iNLC), reprogrammed from fibroblasts from 12 patients with BD using label-free live optical imaging based on a nanostructured photonic crystal biosensor, is presented. They found that changes in the peak wavelength value (PWV), which is a measure of cell adhesion, were associated with patient intrinsic lithium response, and not with lithium exposure alone. Cells derived from patients referred as lithium non-responders were defined as less adherent, compared with cells from lithium responders. Cells from 6 control subjects were found intermediate in adhesion measurement. The authors conclude that pivotal molecular mechanisms involved in the cell-adhesion feature, as measured by the PWV signal, are integrin-CAM interactions.

The study by Madison et al. [83] applied a family-based paradigm involving iPSC lines derived from fibroblasts of two brothers with bipolar disorder, and their two healthy parents. iPSC, upon direct differentiation to the neural lineage, revealed several neurodevelopmental phenotypes and specific defects in gene expression connected with neurogenesis and neuroplasticity, including Wnt pathway components and ion channel subunits. The authors observed that BD patients produce more peripheral nervous system progenitors than central nervous system (CNS) progenitors as measured by CXCR4 expression (a marker of CNS progenitors). Subsequently, $CXCR4^{+}$ neural progenitor cell (NPC) proliferation deficits were rescued by GSK-3 inhibitor (CHIR-99021) treatment, which increased the expression of the β-catenin target genes and the activated Wnt pathway.

Viswanath et al. [84] carried out a systematic review of 85 articles on the application of cellular models in order to study BD pathophysiology including lymphoblastoid cell lines, fibroblasts, olfactory neuronal epithelium and neurons reprogrammed from iPSC. They found that the most frequently replicated findings were disturbances in calcium signaling, the endoplasmic reticulum (ER) stress response, the mitochondrial oxidative pathway, membrane ion channels and the circadian system and apoptosis related genes. These abnormalities were exacerbated by cellular

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005

stressors (e.g. oxidative stress) and were often reversed by *in vitro* lithium treatment.

Concluding remarks

Recently, a team of researchers from Szczecin, Poland, presented a review of stem cell research in the context of its growing impact on contemporary psychiatry [85]. In a separate paper, they described a rare population of early developmental very small embryonic-like stem cells (VSELs) in peripheral blood, suggesting their role in remodeling of the brain in patients with schizophrenia and identifying potential markers of the first psychotic episode. They also found that neuroleptic treatment does not affect the mobilization of VSELs [86] and that enhanced vegetative nervous system tonus has no positive effect on HSC and progenitor cells mobilization in patients suffering from acute psychotic syndromes [87].

The course and treatment of bipolar disorder has been intensively studied in recent years [88]. The use of lithium, the unique drug for this condition, is a cornerstone for the long-term treatment of BD [89]. In the twenty-first century lithium also found its full place in stem cell research. In the 1970s and 1980s the effects of lithium on haematopoietic stem cells began to be studied and these have now been complemented by studies on neural and mesenchymal stem cells. The results obtained so far provide interesting clues as to the mechanism of action of this ion and also to the pathogenesis of BD. It is possible that future research may also contribute to a potential use of stem cells in the treatment of neuropsychiatric conditions.

Role of funding source

The study was not supported by any funding source.

Conflict of interest

All authors declare no conflict of interest that could influence their work.

Q3 Uncited reference

[5].

Acknowledgement

Thanks are due to Prof. Geoffrey Shaw for linguistic consultation of the paper.

Q4 References

[1] Cade J. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;2(10):349–52.
[2] Radomski J, Fuyat HN, Nelson AA, Smith PK. The toxic effects, excretion and distribution of lithium chloride. J Pharmacol Exp Ther 1950;100(4:1):429–40.
[3] Ratajczak MZ, Suszyńska M. Quo Vadis regenerative medicine? Acta Hematol Pol 2013;44(3):161–70.
[4] Kozłowska-Skrzypczak M, Komarnicki M. Hematopoietic stem cells and hematopoiesis. Diagn Lab 2008;44:231–9.
[5] da Silva Meirelles L, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. Stem Cells 2008;26(9):2287–99.
[6] Kemperamann G. Adult neurogenesis. New York: Oxford University Press; 2006.
[7] Mayfield D, Brown RG. The clinical laboratory and electroencephalographic effects of lithium. J Psychiatric Res 1966;4(3):207.
[8] Murphy DL, Goodwin FK, Bunney Jr WE. Leukocytosis during lithium treatment. Am J Psychiatry 1971;127(11):1559–61.
[9] Ozdemir MA, Sofuoğlu S, Tanrikulu G, Aldanmaz F, Eşel E, Dündar S. Lithium-induced hematologic changes in patients with bipolar affective disorder. Biol Psychiatry 1994;35(3):210–3.
[10] Hammond WP, Dale DC. Lithium therapy of canine cyclic hematopoiesis. Blood 1980;55(1):26–8.
[11] Levitt L, Quesenberry P. The effect of lithium on murine hematopoiesis in a liquid culture system. N Engl J Med 1980;302(13):713–9.
[12] Gallicchio VS, Chen MG. Modulation of murine pluripotential stem cell proliferation in vivo by lithium carbonate. Blood 1980;56(6):1150–2.
[13] Joyce RA. Sequential effects of lithium on haematopoiesis. Br J Haematol 1984;56(2):307–21.
[14] Ballin A, Lehman D, Sirota P, Litvinjuk U, Meyte D. Increased number of peripheral blood CD34+ cells in lithium treated patients. Br J Haematol 1998;100(1):219–21.
[15] Huang J, Nguyen-McCarty M, Hexner EO, Danet-Desnoyers G, Klein PS. Maintenance of hematopoietic stem cells through regulation of Wnt and mTOR pathways. Nat Med 2012;18(12):1778–85.
[16] Walasek MA, Bystrykh L, van den Boom V, Olthof S, Ausema A, Ritsema M, et al. The combination of valproic acid and lithium delays hematopoietic stem/progenitor cell differentiation. Blood 2012;119(13):3050–9.
[17] Petrini M, Vaglini M, Carulli G, Azzara A, Ambrogi F, Bertelli A. Effects of lithium and rubidium on the differentiation of mononuclear cells. Int J Tissue React 1986;8(5):391–2.
[18] Harker WG, Rothstein G, Clarkson D, Athens JW, Macfarlane JL. Enhancement of colony-stimulating activity production by lithium. Blood 1977;49(2):263–7.
[19] Turner A, Allalunis M. Mononuclear cell production of colony-stimulating activity in humans taking oral lithium carbonate. Blood 1978;52:234.
[20] Gamba-Vitalo C, Gallicchio VS, Watts TD, Chen MG. Lithium stimulated in vitro megakaryocytopoiesis. Exp Hematol 1983;11(5):382–8.
[21] Eslaminejad MB, Karimi N, Shahhoseini M. Chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells treated by GSK-3 inhibitors. Histochem Cell Biol 2013;140(6):623–33.
[22] Kapadia RM, Guntur AR, Reinhold MI, Naski MC. Glycogen synthase kinase 3 controls endochondral bone development: contribution of fibroblast growth factor 18. Dev Biol 2005;285(2):496–507.
[23] Kawata K, Kubota S, Eguchi T, Moritani NH, Shimo T, Kondo S, et al. Role of the low-density lipoprotein receptor-related protein-1 in regulation of chondrocyte differentiation. J Cell Physiol 2010;222(1):138–48.
[24] de Boer J, Wang HJ, Van Blitterswijk C. Effects of Wnt signaling on proliferation and differentiation of human mesenchymal stem cells. Tissue Eng 2004;10(3–4):393–401.
[25] de Boer J, Siddappa R, Gaspar C, van Apeldoorn A, Fodde R, van Blitterswijk C. Wnt signaling inhibits osteogenic differentiation of human mesenchymal stem cells. Bone 2004;34(5):818–26.
[26] Clément-Lacroix P, Ai M, Morvan F, Roman-Roman S, Vayssière B, Belleville C, et al. Lrp5-independent activation of Wnt signaling by lithium chloride increases bone formation and bone mass in mice. Proc Natl Acad Sci U S A 2005;102(48):17406–11.
[27] Chen Y, Whetstone HC, Lin AC, Nadesan P, Wei Q, Poon R, et al. Beta-catenin signaling plays a disparate role in different phases of fracture repair: implications for therapy to improve bone healing. PLoS Med 2007;4(7):249.
[28] Edwards CM, Edwards JR, Lwin ST, Lwin ST, Esparza J, Oyajobi BO, et al. Increasing Wnt signaling in the bone marrow microenvironment inhibits the development of myeloma bone disease and reduces tumor burden in bonein vivo. Blood 2008;111(5):2833–42.
[29] Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. J Clin Psychopharmacol 2008;28(4):384–91.
[30] Vestergaard P, Rejnmark L, Mosekilde L. Reduced relative risk of fractures among users of lithium. Calcif Tissue Int 2005;77(1):1–8.
[31] Zamani A, Omrani GR, Nasab MM. Lithium's effect on bone mineral density. Bone 2009;44(2):331–4.
[32] Satija NK, Sharma D, Afrin F, Tripathi RP, Gangenahalli G. High throughput transcriptome profiling of lithium stimulated human mesenchymal stem cells reveals priming towards osteoblastic lineage. PLoS One 2013;8(1):e55769.
[33] Tsai LK, Wang Z, Munasinghe J, Leng Y, Leeds P, Chuang DM. Mesenchymal stem cells primed with valproate and lithium robustly migrate to infarcted regions and facilitate recovery in a stroke model. Stroke 2011;42(10):2932–9.
[34] Yoshino JE, DeVries GH. Effect of lithium on Schwann cell proliferation stimulated by axolemma- and myelin-enriched fractions. J Neurochem 1987;48(4):1270–7.
[35] Kim JS, Chang MY, Yu IT, Kim JH, Lee SH, Lee YS, et al. Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both in vitro and in vivo. J Neurochem 2004;89(2):324–36.
[36] Son H, Yu IT, Hwang SJ, Kim JS, Lee SH, Lee YS, et al. Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. J Neurochem 2003;85(4):872–81.
[37] Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. J Neurochem 2000;75(4):1729–34.
[38] Li H, Li Q, Du X, Sun Y, Wang X, Kroemer G, et al. Lithium-mediated long-term neuroprotection in neonatal rat hypoxia–ischemia is associated with antiinflammatory effects and enhanced proliferation and survival of neural stem/progenitor cells. J Cereb Blood Flow Metab 2011;31(10):2106–15.
[39] Kang K, Kim YJ, Kim YH, Roh JN, Nam JM, Kim PY, et al. Lithium pretreatment reduces brain injury after intracerebral hemorrhage in rats. Neurol Res 2012;34(5):447–54.
[40] Huo K, Sun Y, Li H, Du X, Wang X, Karlsson N, et al. Lithium reduced neural progenitor apoptosis in the hippocampus and ameliorated functional deficits after irradiation to the immature mouse brain. Mol Cell Neurosci 2012;51(1–2):32–42.

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005

[41] O'Leary OF, O'Connor RM, Cryan JF. Lithium-induced effects on adult hippocampal neurogenesis are topographically segregated along the dorso-ventral axis of stressed mice. Neuropharmacology 2012;62(1):247–55.
[42] Kara N, Narayanan S, Belmaker RH, Einat H, Vaidya VA, Agam G. Chronic lithium treatment enhances the number of quiescent neural progenitors but not the number of DCX-positive immature neurons. Int J Neuropsychopharmacol 2015;18(7). http://dx.doi.org/10.1093/ijnp/pyv003.
[43] Segi-Nishida E, Warner-Schmidt JL, Duman RS. Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. Proc Natl Acad Sci U S A 2008;105(32):11352–57.
[44] Encinas JM, Vaahtokari A, Enikolopov G. Fluoxetine targets early progenitor cells in the adult brain. Proc Natl Acad Sci U S A 2006;103(21):8233–8.
[45] Hill EJ, Nagel DA, O'Neil JD, Torr E, Woehrling EK, Devitt A, et al. Effects of lithium and valproic acid on gene expression and phenotypic markers in an NT2 neurosphere model of neural development. PLoS One 2013;8(3):e58822.
[46] Hasgekar NN, Gokhale PP, Amin MK, Seshadri R, Lalitha VS. Lithium inhibits growth in a murine neural precursor cell line. Cell Biol Int 1996;20(12):781–6.
[47] Misiuta IE, Saporta S, Sanberg PR, Zigova T, Willing AE. Influence of retinoic acid and lithium on proliferation and dopaminergic potential of human NT2 cells. J Neurosci Res 2006;83(March (4)):668–79.
[48] Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT, et al. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. Neuropsychopharmacology 2008;33(2):361–7.
[49] Bearden CE, Thompson PM, Dutton RA, Frey BN, Peluso MA, Nicoletti M, et al. Three-dimensional mapping of hippocampal anatomy in unmedicated and lithium-treated patients with bipolar disorder. Neuropsychopharmacology 2008;33(6):1229–38.
[50] Lyoo IK, Dager SR, Kim JE, Yoon SJ, Friedman SD, Dunner DL, et al. Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: a longitudinal brain imaging study. Neuropsychopharmacology 2010;35(8):1743–50.
[51] Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry 2011;69(4):326–35.
[52] Selek S, Nicoletti M, Zunta-Soares GB, Hatch JP, Nery FG, Matsuo K, et al. A longitudinal study of fronto-limbic brain structures in patients with bipolar I disorder during lithium treatment. J Affect Disord 2013;150(2):629–33.
[53] Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A, et al. Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med 2014;44(3):507–17.
[54] Quiroz JA, Machado-Vieira R, Zarate Jr CA, Manji HK. Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. Neuropsychobiology 2010;62(1):50–60.
[55] Inal-Emiroglu FN, Karabay N, Resmi H, Guleryuz H, Baykara B, Alsen S, et al. Correlations between amygdala volumes and serum levels of BDNF and NGF as a neurobiological markerin adolescents with bipolar disorder. J Affect Disord 2015;182:50–6.
[56] Benedetti F, Poletti S, Radaelli D, Locatelli C, Pirovano A, Lorenzi C, et al. Lithium and GSK-3β promoter gene variants influence cortical gray matter volumes in bipolar disorder. Psychopharmacology (Berl) 2015;232(7):1325–36.
[57] Allagui MS, Nciri R, Rouhaud MF, Murat JC, El Feki A, Croute F, et al. Long-term exposure to low lithium concentrations stimulates proliferation, modifies stress protein expression pattern and enhances resistance to oxidative stress in SH-SY5Y cells. Neurochem Res 2009;34(3):453–62.
[58] Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? Bipolar Disord 2010;12(1):87–94.
[59] Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study. Br J Psychiatry 2015;207(1):46–51.
[60] Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. Br J Psychiatry 2007;190:359–60.
[61] Sofola-Adesakin O, Castillo-Quan JI, Rallis C, Tain LS, Bjedov I, Rogers I, et al. Lithium suppresses Aβ pathology by inhibiting translation in an adult Drosophila model of Alzheimer's disease. Front Aging Neurosci 2014;6:190.
[62] Senatorov VV, Ren M, Kanai H, Wei H, Chuang DM. Short term lithium treatment promotes neuronal survival and proliferation in rat striatum infused with quinolinic acid, an excitotoxic model of Huntington's disease. Mol Psychiatry 2004;9(4):371–85.
[63] Dong B-T, Tu G-J, Han Y-X, Chen Y. Lithium enhances cell proliferation and differentiation of mesenchymal stem cells to neural cells in rat spinal cord. Int J Clin Exp Pathol 2015;8(3):2473–83.
[64] Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12–CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 2006;25(6):977–88.
[65] Kast RE. How lithium treatment generates neutrophilia by enhancing phosphorylation of GSK-3, increasing HIF-1 levels and how this path is important during engraftment. Bone Marrow Transplant 2008;41(1):23–6.
[66] Huang J, Zhang Y, Bersenev A, O'Brien WT, Tong W, Emerson SG, et al. Pivotal role for glycogen synthase kinase-3 in hematopoietic stem cell homeostasis in mice. J Clin Invest 2009;119(12):3519–29.
[67] Hedgepeth C, Conrad LJ, Zhang J, Huang HC, Lee VM, Klein PS. Activation of the Wnt signaling pathway: a molecular mechanism for lithium action. Dev Biol 1997;185(1):82–91.
[68] Stambolic V, Ruel L, Woodgett J. Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. Curr Biol 1996;6(12):1664–8.
[69] Trowbridge JJ, Xenocostas A, Moon RT, Bhatia M. Glycogen synthase kinase-3 is an in vivo regulator of hematopoietic stem cell repopulation. Nat Med 2006;12(1):89–98.
[70] Ying QL, Wray J, Nichols J, Batlle-Morera L, Doble B, Woodgett J, et al. The ground state of embryonic stemβ cell self-renewal. Nature 2008;453(7194):519–23.
[71] Doble BW, Patel S, Wood GA, Kockeritz LK, Woodgett JR. Functional redundancy of GSK-3alpha and GSK-3beta in Wnt/beta-catenin signaling shown by using an allelic series of embryonic stem cell lines. Dev Cell 2007;12(6):957–71.
[72] Miyoshi K, Kasahara K, Miyazaki I, Asanuma M. Lithium treatment elongates primary cilia in the mouse brain and in cultured cells. Biochem Biophys Res Commun 2009;388(4):757–62.
[73] Wexler EM, Geschwind DH, Palmer TD. Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway activation. Mol Psychiatry 2008;13(3):285–92.
[74] Goessling W, North TE, Loewer S, Lord AM, Lee S, Stoick-Cooper CL, et al. Genetic interaction of PGE2 and Wnt signaling regulates developmental specification of stem cells and regeneration. Cell 2009;136(6):1136–47.
[75] Holmes T, O'Brien TA, Knight R, Lindeman R, Shen S, Song E, et al. Glycogen synthase kinase-3beta inhibition preserves hematopoietic stem cell activity and inhibits leukemic cell growth. Stem Cells 2008;26(5):1288–97.
[76] Gallicchio VS. Lithium stimulation of in vitro granulopoiesis: evidence for mediation via sodium transport pathways. Br J Haematol 1986;62(3):455–66.
[77] Inayat M, Gallicchio V. The effects of lithium on the immune system. In: Bauer M, Grof P, Muller-Oerlinghausen B., editors. Lithium in neuropsychiatry: the comprehensive guide. Taylor & Francis; 2006. p. 399–414.
[78] Kleinerman ES, Knowles RD, Blick MB, Zwelling LA. Lithium chloride stimulates human monocytes to secrete tumor necrosis factor/cachectin. J Leukoc Biol 1989;46(5):484–92.
[79] Gallicchio VS, Chen MG, Watts TD. Specificity of lithium (Li+) to enhance the production of colony stimulating factor (GM-CSF) from mitogen-stimulated lymphocytes in vitro. Cell Immunol 1984;85(1):58–66.
[80] Doukas MA, Shadduck RK, Waheed A, Gass C. Lithium stimulation of diffusion chamber colony growth is mediated by factors other than colony-stimulating factor. Int J Cell Cloning 1989;7(3):168–78.
[81] Chen HM, DeLong CJ, Bame M, Rajapakse I, Herron TJ, McInnis MG, et al. Transcripts involved in calcium signaling and telencephalic neuronal fate are altered in induced pluripotent stem cells from bipolar disorder patients. Transl Psychiatry 2014;4:e375.
[82] Wang JL, Shamah SM, Sun AX, Waldman ID, Haggarty SJ, Perlis RH. Label-free, live optical imaging of reprogrammed bipolar disorder patient-derived cells reveals a functional correlate of lithium responsiveness. Transl Psychiatry 2014;4:e428.
[83] Madison JM, Zhou F, Nigam A, Hussain A, Barker DD, Nehme R, et al. Characterization of bipolar disorder patient-specific induced pluripotent stem cells from a family reveals neurodevelopmental and mRNA expression abnormalities. Mol Psychiatry 2015;20(6):703–17.
[84] Viswanath B, Jose SP, Squassina A, Thirthalli J, Purushottam M, Mukherjee O, et al. Cellular models to study bipolar disorder: a systematic review. J Affect Disord 2015;184(1):36–50.
[85] Ratajczak M, Kucharska-Mazur J, Samochowiec J. Stem cell research and its growing impact on contemporary psychiatry. Psychiatr Pol 2014;48(6):1073–85.
[86] Kucharska-Mazur J, Tarnowski M, Dołęgowska B, Budkowska M, Pędziwiatr D, Jabłoński M, et al. Novel evidence for enhanced stem cell trafficking in antipsychotic-naïve subjects during their first psychotic episode. J Psychiatr Res 2014;49(2):18–24.
[87] Kucharska-Mazur J, Pedziwiatr D, Poniewierska A, Tkacz M, Suszynska M, Tarnowski M, et al. A lack of positive effect of enhanced vegetative nervous system tonus on mobilization of hematopoietic stem and progenitor cells in patients suffering from acute psychotic syndromes. Leukemia 2013;27(4):959–61.
[88] Ferensztajn E, Rybakowski J. Staging of bipolar affective illness. Psychiatr Pol 2012;46(4):613–26.
[89] Rybakowski JK. Lithium in neuropsychiatry: a 2010 update. World J Biol Psychiatry 2011;12(5):340–8.

Please cite this article in press as: Ferensztajn-Rochowiak E, Rybakowski JK. The effect of lithium on hematopoietic, mesenchymal and neural stem cells. Pharmacol Rep (2015), http://dx.doi.org/10.1016/j.pharep.2015.09.005