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Review article

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

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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.

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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].

Mesenchymal stem cells (MSC) are characterized by fibroblastic-like morphology and ability to adhere to culture surfaces. MSC, originally isolated from bone marrow, are derived from perivascular cells (pericytes). Perivascular zone is decribed as MSC niche, where MSC can differentiate into mesodermal cell lineage, from progenitors to mature cells, including osteoblasts, chondrocytes, myocytes and adipocytes. *In vitro* studies showed also MSC potential to differentiate into ectodermal and endodermal cell lineages, including neural and glial cells, keratinocytes or hepatocytes. The main function of MSC *in vivo* is to stabilize blood vessels and contribute to tissue homeostasis. They exert paracrine effects and have many immunoregulatory properties, playing an important role during injury, inflammation and tissue repair [5].

Neural SC can differentiate into neurons, astrocytes and oligodendrocytes. The classical scheme presents a development of neural SC 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 SC through ventral and dorsal SC, 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 SC spectrum and the term "neural precursors" for neural SC 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 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 SC 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.