

*Opšti pregledi/  
General reviews*

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LITHIUM: SPECIFICS, TOXICITY AND  
EFFECTS ON THE BLOOD-BRAIN AND  
BLOOD-CEREBROSPINAL FLUID BARRIERS

LITIUM: TOKSIČNOST I EFEKTI NA  
KRVNO-MOŽDANU I KRVNO-LIKVORSKU  
BARIJERU

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*Key words*

lithium characteristics and toxicity,  
blood-brain and blood-cerebrospinal  
fluid barriers.

*Ključne reči*

Karakteristike i toksičnost litijuma,  
krvno-moždana i krvno-likvorska  
barijera.

*Abstract*

In this review, we describe the lithium and its toxicity occurred in patients with bipolar disorder receiving lithium therapy. Part of this review focuses on the effect of the metal-induced neurotoxicity on the blood-brain (BBB) and blood-cerebrospinal fluid (CSF) barriers (BCSFB), which are essential to brain chemical stability in the central nervous system (CNS).

Normally, lithium is not present in significant amount in body fluid (<0.2 mEq/L). However, lithium salts have been used therapeutically for almost 150 years, beginning with its use for the treatment of gout in the 1850s [1]. The use of lithium became problematic and was discarded due to the serious toxicity associated with the widespread use of lithium in tonics, elixirs, and as a salt substitute. It is not known whether lithium has a physiological role in some organisms, but nutritional studies in mammals have indicated its importance to health, leading to suggestion that it can be classed as an essential trace element with an RDI of 1 mg/day. Observational studies in Japan, reported in 2011, suggested that naturally occurring lithium in drinking water may increase human lifespan [2]. Strikingly, no study reported negative effects of lithium. It is the only treatment that has shown efficacy for acute mania and acute depression as well as prevention of recurrent mania and depression [3].

The production by the choroid plexuses of the CSF, its circulation and resorption are unique characteristics of the CNS. In conjunction with the BBB, the BCSFB and the flow dynamic of this fluid are the main elements setting the cerebral availability of drugs. The exchanges between the blood and the CSF across the choroidal epithelium are tightly regulated, in the presence of interepithelial tight junctions, by various transports and metabolic processes [4]. The BBB and the BCSFB are formed by brain endothelial cells and choroid plexus epithelial cells, respectively. Most blood vessels in plexus choroideus are wide-calibers capillaries with thin fenestrated endothelial walls [5, 6].

*INTRODUCTION*

Lithium has been in use since the 1870s. Lithium was initially used to treat depression, gout, and neutropenia, and for cluster headache prophylaxis, but it fell out of favor because of its side effects [7]. In the 1940s, the US Food and Drug Administration (FDA) banned the use of lithium because of fatalities but lifted the ban in 1970 [8, 9, 10].

Presently, lithium is commonly used as maintenance treatment of bipolar disorder [11]. Lithium poi-

soning occurs frequently, since it is used in a population at high risk for overdose. Furthermore, lithium has a relatively narrow therapeutic index that predisposes patients on chronic lithium maintenance treatment to poisoning with relatively minor changes in medications or health status [12]. Lithium is a commonly prescribed pharmacological treatment for mood disorders. However, the use of lithium may be limited by acute and chronic toxic side effects. Acute toxicity almost always manifests as CNS dysfunction, and the degree of toxicity usually parallels the extent of CNS dysfunction.

tion. Chronic toxic manifestations affect cardiac, renal, and endocrine systems [13]. It is associated with a number of side effects and potentially serious toxicity. Prolonged lithium intoxication (>2 mM) can cause permanent brain damage. To date, there is little data on the subject of lithium toxicity and especially the brain. As the integrity of BBB and BCSFB, both structurally and functionally, is essential to brain chemical stability, the role of the choroid plexus in metal-induced neurotoxicities has become an important, yet under-investigated research area in neurotoxicology. Our current knowledge on the toxicological aspect of choroid plexus research is still incomplete. Thus, the future research needs have been suggested to focus on the role of choroid plexus in early CNS development as affected by metal sequestration in this tissue, to explore how metal accumulation alters the capacity of the choroid plexus in regulation of certain essential elements involved in the etiology of neurodegenerative diseases, and to better understand the blood-CSF barrier as a defense mechanism in overall CNS function [14].

This review is focused on the lithium toxicity and its functional role in the homeostatic regulation and responses of the blood-brain barrier and blood-cerebrospinal fluid barrier.

### *About lithium*

Lithium is a soft, silver-white metal that belongs to the alkali metal group of chemical elements. Lithium's name is derived from the Greek word "lithos", meaning "stone". Lithium was discovered by Johan Arfvedson in 1817, during an analysis of petalite ( $\text{LiAlSi}_4\text{O}_{10}$ ). Lithium is found in trace amount in numerous plants, plankton, and invertebrates, at concentrations of 69 to 5,760 parts per billion (ppb). In vertebrates the concentration is slightly lower, and nearly all vertebrate tissue and body fluids have been found to contain lithium ranging from 21 to 763 ppb.

### *Characteristics*

Lithium is the least dense of the metals. It is highly reactive and does not occur freely in nature. Freshly cut surfaces oxidize rapidly in air to form a black oxide coating. It is the only common metal that reacts with nitrogen at room temperature, forming lithium nitride. Lithium burns with a crimson flame, but when the metal burns sufficiently well, the flame becomes a brilliant white. Lithium has a high specific heat capacity and it exists as a liquid over a wide temperature range.

### *Interesting facts about lithium*

Lithium is believed to be one of only three elements - the others are hydrogen and helium - produced in significant quantities by the Big Bang. Lithium is the only alkali metal that reacts with nitrogen. Humphrey Davy produced some of the world's first

lithium metal from lithium carbonate. Today lithium carbonate - or more precisely the lithium ions in lithium carbonate - are used to inhibit the manic phase of bipolar (manic-depressive) disorder. Batteries based on lithium have revolutionized consumer devices such as computers and cell phones. For a given battery weight, lithium batteries pack a lot of energy compared with batteries based on other metals; in other words, lithium batteries have high energy density.

### *Lithium uses*

Pure lithium metal is used in rechargeable lithium ion batteries and the metal is used as an alloy with aluminum, copper, manganese, and cadmium to make high performance aircraft parts. Lithium also has various nuclear applications, for example as a coolant in nuclear breeder reactors and a source of tritium, which is formed by bombarding lithium with neutrons. Lithium chloride and bromide are used as desiccants. Lithium stearate is used as an all-purpose and high-temperature lubricant [15]. Lithium carbonate is used as a mood-stabilizing drug. It is successful in improving both the manic and depressive symptoms in 70 to 80% of patients [16]. Lithium may also be used to treat alcoholism, schizoaffective disorders, and cluster headaches [17].

### *Harmful effects*

Lithium is corrosive, causing skin burns as a result of the caustic hydroxide produced in contact with moisture. Women taking lithium carbonate for bipolar disorder may be advised to vary their treatment during pregnancy as lithium may cause birth defects.

### *Lithium toxicity and clinical presentation of lithium intoxication*

Lithium effect has been studied extensively for almost 60 years because of its use in treating manic-depressive illness. It is associated with a number of side effects and potentially serious toxicity.

The central nervous system is the major organ system affected, although the renal, gastrointestinal (GI), endocrine, and cardiovascular systems also may be involved. Lithium is available only for oral administration. It is almost completely absorbed from the GI tract. Peak levels occur 2-4 hours post-ingestion, although absorption can be much slower in massive overdose or with ingestion of sustained-release preparations. Neurologic effects of lithium toxicity include tremors, lethargy, confusion, seizures, and coma. GI effects of lithium toxicity include nausea, vomiting, crampy abdominal pain, and diarrhea. Mild-to-moderate lithium toxicity is characterized by tremor, weakness, and mild confusion. Moderate-to-severe lithium toxicity is characterized by altered mental status, muscle fasciculations, stupor, seizures, coma, hyperreflexia, and cardiovascular collapse [12].

Psychiatrists define mood disorders as a group of mental disorders in which disturbance of mood is accompanied by either a full or partial manic or depressive syndrome that is not due to any other mental disorder. Three main categories of patients who are poisoned are as follows: acute, acute-on-chronic, and chronic.

**Acute:** These patients usually do not have a tissue body burden and symptoms are predominately GI including nausea, vomiting, cramping, and sometimes diarrhea. Progression of acute toxicity can involve neuromuscular signs such as tremulousness, dystonia, hyperreflexia, and ataxia. Cardiac dysrhythmias have been reported but rarely occur. The most common ECG finding is T-wave flattening [18-19].

**Acute-on-chronic:** These patients take lithium regularly and have taken a larger dose recently. These patients may display both GI and neurologic symptoms, and serum levels can be difficult to interpret. Patients should be treated according to their clinical manifestations. **Chronic:** These patients typically have a large body burden of lithium and may be difficult to treat. Chronic lithium toxicity is usually precipitated with introduction of new medication that may impair renal function/excretion or cause a hypovolemic state. Symptoms are primarily neurologic. Mental status is often altered and can progress to coma and seizures if the diagnosis is unrecognized. Many severely poisoned patients can develop a syndrome of irreversible lithium-effectuated neurotoxicity such as cognitive impairment, sensorimotor peripheral neuropathy, and cerebellar dysfunction [12].

Lithium functions as a mood stabilizer in patients with bipolar disorders. Approximately 80% of manic patients respond to acute lithium treatment [20]. In addition, lithium is administered for prophylactic treatment of bipolar disorders even though its narrow therapeutic range (0.6-1.2 mEq/L) increases the potential for toxicity [21-22]. Side effects of lithium generally correlate with the patient's serum level and often involve the CNS. Severe neurologic sequelae may occur in patients who take overdoses.

### *Physiology*

Lithium affects ion transport and cell membrane potential by competing with sodium and potassium and thus providing a pathway for lithium entry into cells; these effects may alter neuronal function. The pathways for transporting lithium out of cells are more limited, resulting in lithium accumulating intracellular. It is important to realize that lithium does not equilibrate passively between intracellular and extracellular compartments. If lithium equilibrated passively across cell membranes, the lithium cell-to-plasma concentration ratio would be approximately 10 to 30 because of the negative membrane potential of most cells. However,

the measured cell-to-plasma lithium concentration ratio is actually much lower. For example, a ratio of 2 to 4 is found in rat vascular smooth cells, rat brain slices, cultured neuroblastoma cells, and rat skeletal muscle cells [23]. Thus, lithium must be actively transported out of most cells [24]. Wraae found a greater concentration of lithium in the CSF than that of the brain for 2 h after single intraperitoneal injection of lithium chloride. This result is consistent with passive transfer kinetics of lithium in the CSF and elimination of lithium from the cerebral tissue via the CSF [25].

Lithium also alters neurotransmitter activity, enhances the effects of serotonin and acetylcholine, reduces the effects of dopamine, has variable effects on norepinephrine, inhibits inositol metabolism, and prevents the accumulation of cyclic adenosine 5'-monophosphate. These secondary messengers (inositol and cyclic adenosine 5'-monophosphate) work through the G protein system, and alterations in their metabolism and intracellular levels probably influence neurotransmitter activity [26].

### *Lithium and blood-brain and blood-cerebrospinal fluid barriers*

The chemical stability in the brain underlies normal human thinking, learning, and behavior. The BBB and the BCSFB are formed by brain endothelial cells and choroid plexus epithelial cells, respectively (Fig. 1). The BBB and BCSFB are not only anatomical barriers, but also dynamic tissues that express multiple transporters, receptors and enzymes. The two main functions of these barriers are to impede free diffusion between brain fluids and blood and to provide transport processes for essential nutrients, ions and waste products. The tight junctions between cerebral endothelial cells at the blood-brain interface and between the choroid plexus epithelial cells represent the structural basis of these barriers and permit the brain to function in a highly regulated and stable environment [27]. Plexus choroideus is an intraventricular brain structure involved in the production of CSF and in the synthesis and transport of numerous CSF components. The surface of the choroid plexus consists of numerous villi each covered with single layer of epithelial cells surrounded by vascular connective tissue cells (Fig. 1 A). These cells are generally considered to be modified ependymal cells with epithelial cell characteristics and referred to as choroidal light and dark epithelial cells (average size 13  $\mu\text{m}$ ) (Fig. 1 B) [28]. As a secretory source of vitamins, peptides and hormones for neurons, the choroid plexus provides substances for brain homeostasis [29]. Most blood vessels in plexus choroideus are wide-calibers capillaries (mean luminal diameter 9.16  $\mu\text{m}$ ) with thin fenestrated endothelial walls (Fig. 1 C) [5, 6].

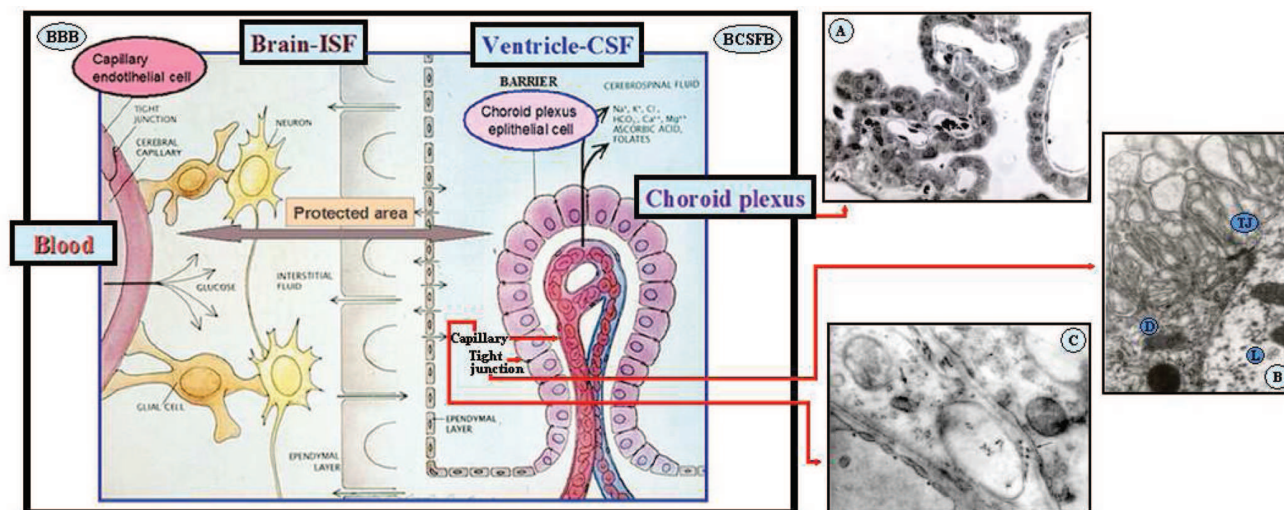


Fig.1. Schematic drawing of blood-brain (BBB) and blood-cerebrospinal fluid barrier (BCSFB) with micrograph (A) and electron micrographs (B, C) of rat choroid plexus. Essential nutrients reach the neurons and glial cells in the brain by crossing either BCSFB, which is regulated by the choroid plexus, or the BBB of the cerebral capillaries. Water-soluble molecules cannot diffuse freely between the blood and the CSF because of impermeable tight junction (TJ) seals between the light (L) and dark (D) choroid plexus epithelial cells; instead the epithelial cells transfer certain molecules from one side of the barrier to the other. Similarly, wastes in the interstitial fluid (ISF) can pass into the CSF for disposal. The endothelial cells of the cerebral capillaries, which are also sealed by tight junctions, control the direct exchange of materials between the blood and ISF. [Modified from Spector R, Johanson CE: *The Mammalian Choroid Plexus*, *Sci Am*, 1989, 261: 68-74 and supplemented by authors].

Lithium ions are rapidly absorbed from the gastrointestinal tract and plasma lithium peaks are reached 2 to 4 hours after lithium administration. The distribution of lithium in the body approximates that of total body water, but its passage across the BBB is slow and at equilibration the CSF lithium level reaches only approximately half the plasma concentration. The elimination half-life of lithium averages 20 to 24 hours. Half-life in geriatric patients and patients with impaired renal function is increased, 36 and 40 to 50 hours have been reported respectively [30].

Lithium is distributed in many tissues in the body and excreted almost entirely by the kidney. In most tissues the tissue/serum concentration ratio are less than 1. Values of greater than 1, indicating lithium accumulation, are found in bone, thyroid, and salivary gland. Although Radomski et al [31] found even distribution in serum, heart, kidney, muscle, liver, brain, and adrenal glands of dogs, Davenport [32] showed that lithium concentration varied considerably in different tissues in the rat 1 h after intraperitoneal injection. At that time, lithium concentration in muscle was only 43% of that in serum, but was 5 times the brain lithium concentration. These data were amplified by Schou [33] who showed in rats given lithium intravenously that the ion entered the kidney very rapidly and the brain slowly. Thus, the time to maximum tissue concentration was 15 min for kidney and 22-26 hr for brain. The time for liver, bone, and muscle were 1, 3 and 4 hr, respectively.

The physiological basis of lithium pharmacokinetics in the CSF has been studied in the rat by Wraae [25] and in vivo isolated cat choroid plexus by Yen and

Reed [34]. In this preparation, the blood and nerve supply of the choroid plexus is intact. The data for the rat experiments suggest that lithium is eliminated from cerebral tissue via the CSF rather than through the BBB. The results of the choroid plexus infusion studies suggest that the limited transport of lithium across the choroid plexus by the sodium pump (which normally secretes into the CSF) could produce a lower concentration of lithium in the CSF than in the plasma. The data also confirmed the finding in humans of a high correlation between the steady-state lithium serum concentration and that in the CSF, since the lithium concentration of the fluid bathing the isolated choroid plexus was less than, but correlated with, that in the serum. Thus, lithium enters the CSF by the choroid plexus and then probably by passive diffusion into the brain. It lives the brain by unknown mechanisms (probably diffusion). It does not appear to be removed from the CSF by an active process – at least not by the system that regulates CSF potassium [35].

Lithium was passively transported across the choroid plexus (frog choroid plexus), and Ehrlich and Wright [36] suggest that the major transport pathway is through the tight junctions. The authors suggest the existence of sodium/lithium countertransport in the epithelial cell membranes. The central mechanisms by which lithium exerts its clinical effects on extremes of mood are not fully understood. Lithium affects the brain's monoaminergic neurotransmitter concentrations at the synapse, has strong effects on biologic membranes, and intracellularly inhibits the conversion of inositol monophosphate to free inositol. The latter effect may, in turn, reduce neuronal excitability [37].

The effects of chronic treatment with imipramine or lithium on serotonin (5-HT) receptor subtypes were analyzed in the frontal cortex, hippocampus and choroid plexus of rat brain by quantitative receptor autoradiographic procedures, using radioligands. Lithium (2 mEq/kg/day for 21 days) also decreased the densities of 5-HT<sub>1</sub>, 5-HT<sub>1C</sub> and 5-HT<sub>2</sub> sites in the frontal cortex, and the densities of those including 5-HT<sub>1A</sub> sites in the hippocampus and choroid plexus. Imipramine and lithium very markedly decreased the density of 5-HT<sub>1C</sub> sites in the choroid plexus [38]. Lithium can be transported by both systems to a limited extent and the presence of lithium in the CSF stimulates the sodium-potassium regulating pump [39].

The production by the choroid plexuses of the CSF, its circulation and resorption are unique characteristics of the CNS. In conjunction with the BBB, the BCSFB and the flow dynamic of this fluid are the main elements setting the cerebral availability of drugs. The exchanges between the blood and the cerebrospinal fluid across the choroidal epithelium are tightly regulated, in the presence of interepithelial tight junctions, by various transport and metabolic processes. Strazielle et al describe the different pathways of biotransformation present at the choroid plexus for drug and toxic compounds, and review the evidence that they indeed can act as a mechanism of neuroprotection [4].

The choroid plexus has the capability to modulate drug delivery to the CSF and to participate in the overall cerebral biodisposition of drugs. The specific morphological properties of the choroidal epithelium and the existence of a CSF pathway for drug distribu-

tion to different targets in the CNS suggest that the choroid plexus-CSF route is more significant than previously thought for brain drug delivery. In contrast to its role in CSF penetration of drugs, choroid plexus is also involved in brain protection in that it has the capacity to clear the CSF from numerous potentially harmful CSF-borne exogenous and endogenous organic compounds into the blood. Furthermore, choroid plexus harbors a large panel of drug-metabolizing enzymes as well as transport proteins of the multidrug resistance phenotype, which modulate the cerebral bioavailability of drugs and toxins. The use of an in vitro model of the choroidal epithelium suitable for drug transport studies has allowed the demonstration of the choroidal epithelium acting as an effective metabolic BCSFB toward some xenobiotics, and that a vectorial, blood-facing efflux of conjugated metabolites occurs at the choroidal epithelium [40].

The future investigations need to focus on the role of choroid plexus and brain vessels in early neurodegenerative diseases, and to better understand the BCSFB and BBB as a defense mechanism in overall CNS function.

### *Acknowledgements*

We would like to thank Dr. Ivan S. Ormandzhiev, PhD for helpful discussions and assistance in preparation of this manuscript. The authors greatly appreciate the help provided by Slavko I. Ormandzhiev in adapting and reproducing Fig. 1.

### *Apstrakt*

U ovom radu je opisana primena litijuma i njegova toksičnost u pacijenata sa bipolarnom bolešću koji su na terapiji ovim lekom. Deo ovog rada prikazuje efekte metal-indukovane neurotoksičnosti na krvno-moždanu barijeru i barijeru između krvi i cerebrospinalne tečnosti, koje su esencijalne na moždano hemijsku stabilnost u centralnom nervnom sistemu.

Normalne vrednosti litijuma u telesnim tečnostima nisu u tako značajnim koncentracijama (<0,2 mEq/L). Međutim, litijumove soli se u terapijske svrhe primenjuju gotovo 150 godina, počevši od 1850tih u terapiji gihta. Primena litijuma je postala problematična i izbačena bog ozbiljne toksičnosti udružene sa širokom upotrebom litijuma u tonicima, eliksirima i zameni za so. Nije poznato da li litijum ima fiziološku ulogu u nekim organizmima, ali nutritivne studije na sisarima pokazuju njegov značaj za zdravlje, što dovodi do zaključka da može biti klasifikovan kao esencijalni element sa (preporučenim dnevnim unosom) RDI od 1 mg/dan.

Studije sprovedene u Japanu (2011.) sugerišu da litijum koji je normalno prisutan u pijaćoj vodi može da produži životni vek. Zanimljivo je da ne postoje podaci o negativnim efektima litijuma. Njegova primena je jedina efikasna u lečenju akutnih manija i akutnih depresija, kao i u prevenciji rekurentnih manija i depresija. Produkcija cerebrospinalne tečnosti od strane horioidnog pleksusa, njena cirkulacija i resorpcija je jedinstvena karakteristika CNS. Zajedno sa krvno-moždanom barijerom, barijera krv-cerebrospinalna tečnost i dinamički protok ovih tečnosti su glavni elementi cerebralne dostupnosti lekova. Razmena između krvi i cerebrospinalne tečnosti kroz horioidni epitel je snažno regulisana u prisustvu čvrstih interepitelijalnih veza različitim transportnim i metaboličkim procesima. Krvno-moždana barijera i barijera između krvi i cerebrospinalne tečnosti se formiraju pomoću moždanih endotelne ćelija i epitelne ćelije horioidnog pleksusa. Većina krvnih sudova u horioidnom pleksusu je širokog dijametra kapilara sa tankim šupljikavim endotelne zidovima.

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