Progress in Neuropsychopharmacology & Biological Psychiatry 102 (2020) 109953

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Na^+/K^+-ATPase and lipid peroxidation in forebrain cortex and hippocampus of sleep-deprived rats treated with therapeutic lithium concentration for different periods of time

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ARTICLE INFO

Keywords:
Lithium
Sleep deprivation
Na^+/K^+-ATPase
Lipid peroxidation
Rat brain

ABSTRACT

Lithium (Li) is a typical mood stabilizer and the first choice for treatment of bipolar disorder (BD). Despite an extensive clinical use of Li, its mechanisms of action remain widely different and debated. In this work, we studied the time-course of the therapeutic Li effects on ouabain-sensitive Na^+/K^+-ATPase in forebrain cortex and hippocampus of rats exposed to 3-day sleep deprivation (SD). We also monitored lipid peroxidation as malondialdehyde (MDA) production. In samples of plasma collected from all experimental groups of animals, Li concentrations were followed by ICP-MS.

The acute (1 day), short-term (7 days) and chronic (28 days) treatment of rats with Li resulted in large decrease of Na^+/K^+-ATPase activity in both brain parts. At the same time, SD of control, Li-untreated rats increased Na^+/K^+-ATPase along with increased production of MDA. The SD-induced increase of Na^+/K^+-ATPase and MDA was attenuated in Li-treated rats.

While SD results in a positive change of Na^+/K^+-ATPase, the inhibitory effect of Li treatment may be interpreted as a pharmacological mechanism causing a normalization of the stress-induced shift and return the Na^+/K^+-ATPase back to control level.

We conclude that SD alone up-regulates Na^+/K^+-ATPase together with increased peroxidative damage of lipids. Chronic treatment of rats with Li before SD, protects the brain tissue against this type of damage and decreases Na^+/K^+-ATPase level back to control level.

1. Introduction

Lithium (Li) is a typical mood stabilizer and the first-line treatment of bipolar disorder (BD) according to the accepted treatment guidelines. Only a subset of patients, however, shows a therapeutic response to Li as individual responsiveness to Li is variable (Hou et al., 2016). Despite an extensive clinical use of Li, many widely different mechanisms of action by which this small monovalent ion exerts its therapeutic effects were suggested (Alda, 2015; Can et al., 2014; Vosahlikova and Svoboda, 2016) and no reliable markers exist for diagnosis, monitoring, treatment selection and prognosis of BD (Alda, 2015).

The effects of Li are not easy to categorise. It appears to regulate multiple steps in cellular processes, including the G protein coupled receptor-stimulated signalling and G proteins (Avissar and Schreiber, 2006) alteration of function of immune system (Young, 2009), changes in production of neurotrophic factors in the CNS and periphery (Young, 2009), alteration of composition of brain membrane lipids (Fisar et al., 2005; Lopez-Corcuera et al., 1988; Muller et al., 2015), decrease of

Abbreviations: AA, arachidonic acid; ASC, ascorbic acid; Ab, antibody; BD, bipolar disorder; BP, bipolar; FBC, forebrain cortex; HIP, hippocampus; ICP-MS, inductively coupled plasma mass spectrometry; Li, lithium; LP, lipid peroxidation; MDA, malondialdehyde; P_i, inorganic phosphate; PNS, post nuclear supernatant; REM, rapid eye movement; SD, sleep deprivation; TBARS, thiobarbituric acid reactive substances

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https://doi.org/10.1016/j.pnpbp.2020.109953
Received 31 October 2019; Received in revised form 22 April 2020; Accepted 27 April 2020
Available online 29 April 2020

arachidonic acid (AA) turnover in brain phospholipids (Rapoport et al., 2009) or induction of oxidative stress (Catalá, 2009; Suwalsky et al., 2007).

One of the oldest candidate pathways of Li action is the regulation of ouabain-sensitive Na^+/K^+-ATPase activity and disturbance of homeostasis of intracellular concentrations of Na^+, K^+, Ca^{2+} and chloride ions (El-Mallakh, 2004). The results of studies performed in this area on both human blood cells and rat brains have produced contradictory results. Decreased Na^+/K^+-ATPase in patients undergoing the acute manic phase of BD was reported by Hesketh et al. (1977), Naylor et al. (1980) and Reddy et al. (1992). Bech et al. (1978) and Johnston et al. (1980) described an increase of Na^+/K^+-ATPase in erythrocytes prepared from Li-treated patients when compared with Li-untreated ones. The increase of [^{3}H]ouabain binding capacity in lymphocytes isolated from healthy volunteers taking oral lithium carbonate was reported by Antia et al. (1992). A decreased expression level of α1-subunit of Na^+/K^+-ATPase in post-mortem samples of temporal cortex of bipolar (BP) individuals was reported by Rose et al. (1998) and Tochigi et al. (2008). A strong support for the direct correlation between Na^+/K^+-ATPase and BD was brought by Banerjee et al. (2012) - Na^+/K^+-ATPase activity in erythrocytes collected from 73 BP patients was significantly decreased when compared with erythrocytes obtained from sex and age-matched controls. Lipid peroxidation (LP), measured as TBARS (thiobarbituric acid reactive substances) level in serum of BP patients was increased. Same results were obtained from patients with schizophrenia (Roy et al., 2016). The decrease of Na^+/K^+-ATPase activity in rat brain by chronic Li administration was reported by Guerri et al. (1981). Decreased activity of Na^+/K^+-ATPase was also measured in synaptic plasma membranes prepared from the hippocampus of rats exposed to an experimental model of depression represented by chronic variant stress (de Vasconcellos et al., 2005).

An increasing evidence indicates that oxidative stress and disturbance of antioxidant defence systems play a pivotal role in the biochemical mechanisms underlying a wide range of neuropsychiatric disorders including BD (Zhang and Yao, 2013). In a recent report from the International Society for Bipolar Disorder, the oxidative stress markers were identified as potential biomarkers for BD (Frey et al., 2013) and substances with antioxidant effects are generally considered as potential therapeutics for neuropsychiatric disorders (Pandya et al., 2013). Li was shown to exert the antioxidant and neuroprotective effects by increasing tolerance to oxidative stress in the manic phase of BD (Machado-Vieira et al., 2007). Increased LP and alteration of the major antioxidants enzymes were found in patients with BD and schizophrenia (Kuloglu et al., 2002; Wang et al., 2009). The etiopathology of depression, BD, schizophrenia, and drug addiction were suggested to be jointly related to changes in the composition of brain lipids (Schneider et al., 2017).

Environmental manipulations were often used to induce manic-like states which mimic multiple aspects of BD; one such method is sleep deprivation (SD) (Logan and McClung, 2016; Sharma et al., 2016; Young et al., 2011). The sleep-deprived rodent models provide an important insight into the pathophysiology of mania even though they have some limitations, i.e. especially the fact that this paradigm includes several stressors aside from simple SD (Logan and McClung, 2016). According to one of the latest publications, many changes proceeding in the brain after REM SD may be target of Li action (Andrabi et al., 2019).

In this work, we used sleep-deprived rat model and compared the characteristics of the acute, short-term and chronic effects of Li on forebrain cortex (FBC) and hippocampus (HIP). We selected these two brain parts based on previously published function and/or structure studies related to mood disorders and Li treatment (Andreazza et al., 2008; Frey et al., 2006a, 2006b; Giakoumatos et al., 2015; Rajkowska et al., 2016; Schloesser et al., 2012). To our best knowledge, such investigation has not been done before. The expression level and activity of Na^+/K^+-ATPase were determined in parallel with the intensity of LP measured as production of malondialdehyde (MDA) by HPLC. In blood plasma samples collected from all experimental groups of animals, Li concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS).

2. Material and methods

2.1. Materials and chemicals

[^{3}H]ouabain (30 Ci/mmol, NET211001MC) was purchased from Perkin Elmer (Waltham, Massachusetts, USA). Antibodies Na^+/K^+-ATPase α (H-300: sc-28800), Na^+/K^+-ATPase α (H-3: sc-48345), actin (I-19: sc-1616), β-actin (C4: sc-47778) and goat anti-rabbit IgG-HRP (sc-2004) were from Santa Cruz Biotechnology (Dallas, Texas, USA). Other chemicals were commercially available reagent grade.

2.2. Treatment of rats with clinically relevant concentration of Li

All experiments were approved by Animal Care and Use Committee of the Institute of Physiology of the Czech Academy of Sciences in agreement with Animal Protection Law of the Czech Republic and European Communities Council directives 86/609/EEC. Efforts were made to minimize the number and suffering of animals used.

Adult male Wistar rats (Animal Facility of the Institute of Physiology of the Czech Academy of Sciences) weighing about 200 g were used in this study. The animals were group-housed (2–3 rats per cage) under hygienic conditions in a temperature-controlled room at 22 ± 0.5 °C and relative humidity 50 ± 3% under a 12 h light/dark cycle and with a free access to food and water *ad libitum*. Acclimatization period in the animal room before the start of experiment lasted 3 days. Afterwards, animals were randomly assigned into the experimental groups. Control rats were fed a maintaining diet V1534–000 (SSNIFF Spezialdiäten GmbH, Soest, Germany) without Li (groups C-SD and C + SD). The Li-treated rats were kept on a 0.2% lithium carbonate containing diet (2 g Li_2CO_3/kg, SSNIFF Spezialdiäten GmbH, Soest, Germany) for 1 (acute), 7 (short-term) and 28 (chronic) days (groups Li-SD and Li + SD) (Fukumoto et al., 2001). Food, normal drinking water, and 1.5% NaCl solution were available to all rats *ad libitum*. Detailed information about animal groups is given in Table 1. The final number of rats in each experimental group was 9 (3 rats in 3 independent experiments).

2.3. Sleep deprivation of rats pre-treated with clinically relevant concentration of Li

We used SD as the closest approximation of the pathophysiological

Table 1
Detailed description of all animal groups used in this study.

Group name	1, 7 and 28 days treatment		Sleep deprivation	
	Type of diet	Days	Type of diet	Days, type of cage
Li1 + SD	Li	1	Li	3, SD box
Li1-SD	Li	1	Li	3, standard cage
C1 + SD	C	1	C	3, SD box
C1-SD	C	1	C	3, standard cage
Li7 + SD	Li	7	Li	3, SD box
Li7-SD	Li	7	Li	3, standard cage
C7 + SD	C	7	C	3, SD box
C7-SD	C	7	C	3, standard cage
Li28 + SD	Li	28	Li	3, SD box
Li28-SD	Li	28	Li	3, standard cage
C28 + SD	C	28	C	3, SD box
C28-SD	C	28	C	3, standard cage

C, control diet; Li, 0.2% Li_2CO_3 containing diet; SD, sleep deprivation.

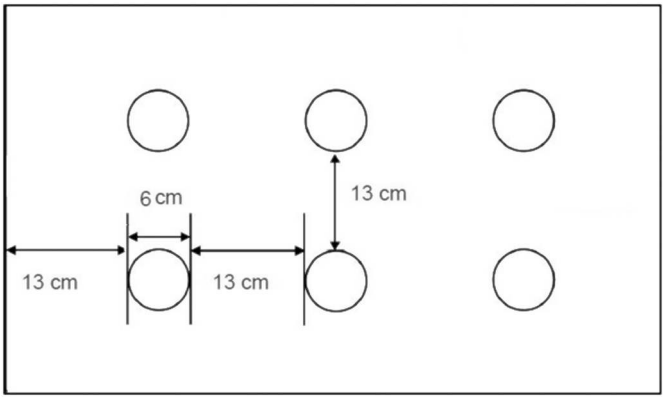

Fig. 1. Sleep deprivation platform module.

state of adult BP patients in the manic phase of disease because lack of sleep and chronobiological dysregulations are considered among the key systemic disruptions of mammalian organism (Landgraf et al., 2014). Paradoxical SD was induced by placing rats onto small platforms surrounded by water. This procedure caused the animal to fall into the water at the onset of REM (rapid eye movement) phase of sleep. SD was performed by the *multiple small platforms* method using sleep deprivation platform module. Dimensions of module and corresponding box were chosen according to Ma et al. (2014), Villafuerte et al. (2015) and Alzoubi et al. (2016). The module (Fig. 1) was placed at the bottom of a plastic box (l × w × h: 79.5 cm × 58 cm × 43.5 cm) filled with water up to 1 cm below the upper surface of the "standing" platforms. All rats were group-housed (2–3 rats per box) and maintained on a 12-h light/dark cycle with normal drinking water, 1.5% NaCl solution and food for 3 days. As SD was carried out for 3 days, the time-frame of the whole experiment was 4 (Li1 ± SD, C1 ± SD), 10 (Li7 ± SD, C7 ± SD) and 31 (Li28 ± SD, C28 ± SD) days, respectively.

Altogether, we studied the following groups of experimental animals: a) Li-treated animals followed by SD - groups Li1 + SD, Li7 + SD, Li28 + SD, b) control, Li-untreated animals followed by SD – groups C1 + SD, C7 + SD, and C28 + SD, c) Li-treated animals (kept in standard cage) without SD - groups Li1-SD, Li7-SD, Li28-SD, d) control animals on control diet without SD - groups C1-SD, C7-SD, and C28-SD (Table 1). The final number of rats in each group was 9 (3 + 3 + 3 rats were used for 3 independent preparations of membranes and PNS from FBC and HIP). It should be noted that rats pre-treated with Li diet for 28 days before SD had a problem to keep balance on the platforms. It was necessary to settle them on the platform several times in the event of their fall into the water.

2.4. Collection of blood and plasma samples and dissection of forebrain cortex and hippocampus

Blood samples from all animals were obtained by cardiac puncture in ether anaesthesia on the last day of experiment. Blood was drawn directly into K3-EDTA-coated vacutainer tubes to prevent coagulation. Samples of blood were centrifuged at 500 × *g* for 10 min. Separate aliquots of blood and plasma were rapidly frozen and stored at −80 °C until further use. Subsequently, rats were killed by decapitation under ether anaesthesia, the whole brains rapidly removed, washed intensively from the remaining blood with ice-cold PBS and FBC and HIP separated from other parts of brain as described in ***2.6***.

2.5. Determination of lithium concentrations by ICP-MS

Plasma Li concentrations were determined as published previously (Vosahlikova et al., 2019, 2018) using Agilent 7700x inductively coupled plasma mass spectrometer with ASX-500 autosampler, equipped with a MicroMist concentric nebulizer and High Matrix Interface. The ICP-MS method conditions are described in details in **Supplementary data *2.5***.

The frozen plasma samples were thawed, vortexed and an aliquot of approximately 0.4 ml was taken and diluted with 10 ml of alkaline solution of 0.5% (m/v) NH_4OH, 0.05% EDTA and 0.05% Triton X-100 in deionized water. Control samples were determined directly at a dilution factor of 25 due to low Li concentrations while the blood samples of rats kept on Li diet were further diluted ten times with the above alkaline solution (dilution factor of 250) to fit into the range of measured calibration.

2.6. Subcellular fractionation of rat forebrain cortex and hippocampus, preparation of post-nuclear supernatant and membrane fractions

Rats were killed by decapitation under ether anaesthesia, the whole brain rapidly removed, washed from blood by ice-cold saline and placed on pre-cooled steel plate (−20 °C) covered with sterile filter paper soaked in ice-cold saline. The forebrain cortex (FBC) and hippocampus (HIP) were separated from thalamus, mesencephalon, pons, medulla oblongata, white matter and other parts of brain as described before (Hejnová et al., 2002; Ihnatovych et al., 2001, 2002a; Ihnatovych et al., 2002b), snap-frozen in liquid nitrogen and stored at −80 °C until use.

Tissue pieces of FBC and HIP were diluted in STEM medium containing 250 mM sucrose, 20 mM Tris–HCl, 3 mM $MgCl_2$, 1 mM EDTA, pH 7.6, fresh 1 mM PMSF and complete protease inhibitor cocktail, homogenized in Teflon-glass homogenizer for 7 min at 1,800 rpm (2 g w.w. per 10 ml) and centrifuged for 7 min at 3,500 rpm (1,200 × g) to separate cell debris and nuclear fraction (remaining in the sediment) from post-nuclear supernatant fraction, PNS (aliquots of PNS used for determination of MDA were frozen in liquid nitrogen and stored at −80 °C). The remaining part of PNS (2/3 by volume) was transferred into a fresh centrifuge tube and centrifuged at 50,000 rpm (200,000 × g) for 30 min. The membrane sediment was re-suspended in TE buffer (50 mM Tris-HCl, 1 mM EDTA, pH 7.6), frozen in liquid nitrogen and stored at −80 °C until further use. From each experimental group of animals (see ***2.2*** and ***2.3***), 3 independent PNS and membrane fractions were made. Protein was determined by the Lowry method using bovine serum albumin as standard.

2.7. [^{3}H]ouabain binding

Na^+/K^+-ATPase content in membranes was determined by binding of radioactively labelled, selective inhibitor of this enzyme, [^{3}H]ouabain, as described before (Roubalova et al., 2015; Vosahlikova et al., 2019; Vosahlikova et al., 2018; Vosahlikova et al., 2017). Membranes (20 μg) were incubated with saturating, 20 nM concentration of [^{3}H] ouabain for 90 min at 30 °C in a total volume of 0.2 ml of 5 mM NaH_2PO_4, 5 mM $MgCl_2$, 50 mM Tris-HCl, pH 7.6. The binding reaction was terminated by dilution with 3 ml of ice-cold Mg-Tris buffer and filtration through Whatman GF/B filters. The filters were washed twice and the radioactivity remaining on the filters was determined by liquid scintillation. Nonspecific binding was determined in the presence of 10 μM unlabelled ouabain. Nonspecific binding represented 99%, 97% and 95% of total binding when determined at 100 μM, 10 μM and 1 μM concentration of unlabelled ouabain, respectively.

2.8. Na^+/K^+-ATPase activity assay

Na^+/K^+-ATPase activity was measured as the production of inorganic phosphate (P_i) according to Baginski et al. (1967) and Kubala et al. (2014). This method is based on the coloured reaction of P_i with ammonium molybdate, which is monitored as absorbance change at 710 nm. ATPase activity was assayed in two reaction media – (A) 130 mM NaCl, 20 mM KCl, 4 mM $MgCl_2$, 3 mM ATP, 30 mM imidazole (pH 7.6) + 0.5 mM ouabain and (B) 130 mM NaCl, 20 mM KCl, 4 mM $MgCl_2$, 3 mM ATP, 30 mM imidazole (pH 7.6), each containing 10 μg of

protein. After 6 min of incubation at 37 °C, the reaction was stopped by the addition of a staining solution composed of 160 mM ascorbic acid, 3.7% (*v*/v) acetic acid, 3% (*w/v*) SDS and 0.5% ammonium molybdate. After 8 min, the staining was stopped by the addition of a solution composed of 0.9% (*w/v*) bismuth citrate, 0.9% (w/v) sodium citrate and 3.7% HCl. Then absorbance at 710 nm was read. Solutions of 0–30 nM KH_2PO_4 were used as a P_i standard. Na^+/K^+-ATPase activity was calculated as the difference between P_i production in assay mix A minus B (A-B) and expressed as μmol P_i released per h per mg of protein.

2.9. Determination of MDA production by HPLC

The concentration of MDA in PNS fractions was determined by reversed-phase high-performance chromatography using Agilent 1100 LC system. 2,4-dinitrophenylhydrazine (DNPH) was used for derivatisation and MDA concentrations were normalized to the total protein contents as described before (Chytilova et al., 2015; Vosahlikova et al., 2019; Vosahlikova et al., 2018). First, 10% v/v Triton X-100 was added to PNS to the final concentration 0.1% v/v. Next, after adding 20 μl of NaOH (6 M) to PNS with Triton X-100 and vortexing, the samples were kept at 60 °C for 30 min followed by 5 min cooling at −20 °C, deproteinised by 50 μl of $HClO_4$ (35% v/v) and centrifuged (15,000 × *g*, 5 min, 4 °C). Supernatant (100 μl) was mixed with 10 μl of DNPH (5 mM) and analysed by an HPLC system (**Supplementary data *2.9***).

2.10. SDS-PAGE and immunoblotting

The α-subunit of Na^+/K^+-ATPase was determined by SDS-PAGE and immunoblotting with polyclonal Ab H300 (sc-28800) or monoclonal H3 (sc-4835) from Santa Cruz. In our hands, both antibodies recognized the single protein with $M_r \approx 90$ kDa in membranes isolated from FBC and HIP of rats of Wistar strain. Polyclonal actin Ab (I-19: sc-1616) and monoclonal β-actin Ab (C4: sc-47778) were used as a loading controls – both Ab recognized the single protein with $M_r \approx 40$ kDa.

The aliquots of PM (20 μg of protein per sample) were mixed 1:1 with 2-fold concentrated Laemmli buffer (SLB) and heated for 3 min at 95 °C. Standard (10% w/v acrylamide/0.26% w/v bis-acrylamide) SDS electrophoresis was carried out as described before (Vosahlikova et al., 2019; Vosahlikova et al., 2018; Vosahlikova et al., 2017) in Mini-PROTEAN® Electrophoresis System (**Supplementary data *2.10***).

2.11. Statistical analysis

Data are presented as mean ± SEM (standard error of the mean). Li concentration in plasma was measured separately in each animal in triplicates. In all other measurements, data were obtained from analysis of 3 independent preparations of PNS or membrane fractions isolated from each group of experimental animals (Table 1). Statistical analysis was carried out by two-way analysis of variance (ANOVA) followed by Bonferroni's post hoc tests (pairwise comparisons; all results excluding immunoblots; 1-day, 7-days and 28-days results were evaluated separately) or unpaired Student's *t*-test (only immunoblots; statistical analysis was based on six immunoblots; the four *sample 1* and four *sample 2* bands were compared in each blot). The differences were considered significant at $p < .05$.

3. Results

3.1. Li concentration in plasma of rats kept on 0.2% lithium carbonate containing diet for 1, 7 or 28 days and after sleep deprivation

The ICP-MS method was used for determination of Li concentrations in plasma samples collected from all experimental groups of rats. Results shown in Table 2, indicated that Li concentrations determined in plasma of rats participating in SD experiments (Li1 + SD, Li7 + SD, Li28 + SD) were in desired therapeutic range - 0.5-1.2 mmol/l (Hiemke et al., 2018) and significantly higher than in rats that were not sleep-deprived (Li1-SD, Li7-SD, Li28-SD). Thus, the therapeutic concentration of Li in plasma was maintained throughout duration of the whole experiment. Increased water consumption (2–3-fold in comparison with control rats) was observed in rats on Li diet after 3–5 days together with increased urinary and stool excretion. Li concentrations in control groups of animals (C1 + SD, C1-SD, C7 + SD, C7-SD, C28 + SD, C28-SD) were less than 0.001 mmol/l.

Table 2
Plasma Li concentration in control (-SD) and sleep-deprived rats (+SD) after 1, 7 and 28 days on 0.2% lithium carbonate containing diet determined by ICP-MS.

Group	Li concentration in plasma [mmol/l]
Li1-SD	0.68 ± 0.05
Li1 + SD	1.05 ± 0.11
Li7-SD	0.64 ± 0.04
Li7 + SD	1.16 ± 0.09
Li28-SD	0.61 ± 0.06
Li28 + SD	0.82 ± 0.10
C1-SD	< 0.001
C1 + SD	< 0.001
C7-SD	< 0.001
C7 + SD	< 0.001
C28-SD	< 0.001
C28 + SD	< 0.001

Results (mean ± SEM) represent the average Li concentration in plasma of 9 animals in each experimental group; all measurements were made in triplicates (detailed description of rats groups in Methods ***2.2*** and ***2.3***).

3.2. Regulation of Na^+/K^+-ATPase in forebrain cortex and hippocampus of rats kept on Li diet for 1, 7 and 28 days and subsequently deprived from sleep for 3 days; determination of [^{3}H]ouabain binding

In FBC, the acute (1 day) treatment of rats with Li resulted in significant decrease of [^{3}H]ouabain binding when compared with corresponding controls (Li1-SD vs. C1-SD, *, $p < .05$), Fig. 2A,Table 3. The same result was found in rats which were treated with Li for 7 (chronic) or 28 days (long-term) – compare Li7-SD vs. C7-SD (**, $p < .01$) and Li28-SD vs. C28-SD (*, $p < .05$). Thus, in membranes prepared from rats treated with therapeutic Li concentration for 1, 7 or 28 days, the number of specific [^{3}H]ouabain binding sites measured at saturating 20 nM concentration, was significantly lower than in membranes prepared from control, Li-untreated rats. Importantly, SD of control, Li-untreated rats resulted in an increase of [^{3}H]ouabain binding when compared with control rats which were not exposed to SD. This increase was noticed in all experimental groups of rats: C1-SD vs. C1 + SD (**, $p < .01$), C7-SD vs. C7 + SD (*, $p < .05$) and C28-SD vs. C28 + SD (**, $p < .01$), Fig. 2A. The increase of [^{3}H]ouabain binding by SD was also detected in Li-treated samples: Li1-SD vs. Li1 + SD (**, $p < .01$), Li7-SD vs. Li7 + SD (*, $p < .05$) and Li28-SD vs. Li28 + SD (*, $p < .05$).

In HIP, the Li-treatment applied for 1 and 7 days before SD did not significantly change [^{3}H]ouabain binding level (Fig. 2B, Table 3). The Li-treatment for 28 days resulted in the increase of this radioligand binding in Li28-SD as well as Li28 + SD samples of HIP when compared with corresponding controls, C28-SD and C28 + SD, respectively (Li28-SD vs. C28-SD, *, $p < .05$; Li28 + SD vs. C28 + SD, *, $p < .05$). As in FBC, the SD of Li-untreated rats was reflected in the increase of [^{3}H]ouabain binding in all experimental groups of animals (C1-SD vs. C1 + SD, **, $p < .01$; C7-SD vs. C7 + SD, *, $p < .05$; C28-SD vs. C28 + SD, *, $p < .05$).

We could therefore, conclude that, 1) in FBC, the treatment of rats with the therapeutic, 1 mM concentration of Li for 1, 7 or 28 days resulted in consistent decrease of [^{3}H]ouabain binding, 2) in HIP, Li-

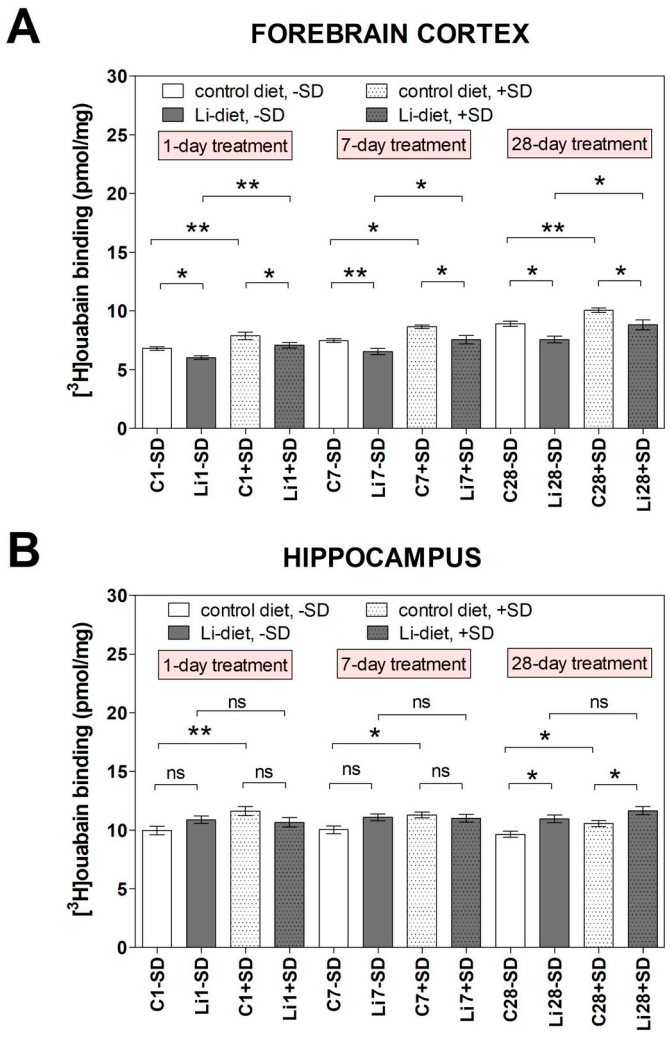

Fig. 2. [^{3}H]ouabain binding in membranes prepared from forebrain cortex (A) and hippocampus (B) of control rats and rats treated with therapeutic Li concentration for 1, 7 and 28 days followed by 3 days of sleep deprivation. Specific binding of [^{3}H]ouabain was measured as described in Methods (**2.7**) in three independent membrane preparations isolated from all groups of experimental animals. Binding assays with each membrane preparation were carried out in three independent membrane preparations in triplicates in each. Specific binding was expressed as pmol/mg of protein. The data represent the means ± SEM. Pairwise comparisons: *, p < .05; **, p < .01; ns, $p > .05$.

treatment for 1 and 7 days was not effective; chronic exposition for 28 days resulted in increase of [^{3}H]ouabain binding, 3) SD of Li-untreated rats enhanced the number of [^{3}H]ouabain binding sites in both FBC and HIP, 4) the stress-induced increase of [^{3}H]ouabain binding was also manifested in membranes prepared from FBC of Li-treated rats, but not in HIP membranes.

3.3. Regulation of Na^+/K^+-ATPase protein level in forebrain cortex of rats kept on Li diet for 1, 7 and 28 days and subsequently deprived from sleep for 3 days; immunoblot analysis of α-subunit

In the next step of our experiments, we determined the protein level of Na^+/K^+-ATPase α subunits in membranes isolated from FBC of all groups of experimental animals. To obtain the best results, i.e. the most accurate quantitative comparison of immunoblot signals between Li-untreated and Li-treated FBC, we used our well established protocol which is based on comparison of control and experimental samples containing exactly the same amount of protein on the same blot. To document visually the efficiency of this approach, typical immunoblots of C1-SD vs. Li1-SD, C7-SD vs. Li7-SD and C28-SD vs. Li28-SD samples are shown in Fig. 3A,Table 4. The typical immunoblots of C1 + SD vs. Li1 + SD, C7 + SD vs. Li7 + SD and C28 + SD vs. Li28 + SD (**B**), C1-SD vs. C1 + SD, C7-SD vs. C7 + SD and C28-SD vs. C28 + SD (**C**) and Li1-SD vs. Li1 + SD, Li7-SD vs. Li7 + SD, Li28-SD vs. Li28 + SD (**D**) are shown in other panels of Fig. 3,Table 4.

Statistical analysis of the difference between each pair of control and Li-treated membranes prepared from each group of experimental animals (1-, 7- and 28-days) was based of six such gels/blots, i.e. comparison of totally 24 (6 × 4) control and 24 (6 × 4) Li-treated immunoblot signals of α-Na^+/K^+-ATPase (Fig. 4A,Table 4). Results of this analysis indicated that the acute (1 day) exposure of rats to Li did not significantly alter Na^+/K^+-ATPase expression level (ns, $p > .05$), however, the short-term (7 days) and chronic (28 days) Li treatment resulted in significant (*, $p < .05$) and highly significant (**, $p < .01$) decrease of Na^+/K^+-ATPase in FBC of these two groups of experimental animals, respectively.

The same results were obtained when immunoblot signals of α-Na^+/K^+-ATPase were compared in C1 + SD vs. Li1 + SD, C7 + SD vs. Li7 + SD and C28 + SD vs. Li28 + SD samples of FBC (Fig. 4B,Table 4). The acute (1 day) exposure did not alter α-Na^+/K^+-ATPase level (ns, p > .05), but the short-term (7 days) and chronic (28 days) Li treatment resulted in significant (*, p < .05) decrease of Na^+/K^+-ATPase in membranes prepared from of sleep-deprived rats.

Comparison of the set of intensities of immunoblot signals of α-Na^+/K^+-ATPase determined in C1-SD vs. C1 + SD, C7-SD vs. C7 + SD and C28-SD vs. C28 + SD samples (Fig. 3C,Table 4) indicated clearly that ***SD alone*** enhanced the α-Na^+/K^+-ATPase level in membranes from FBC of C1 + SD, C7 + SD and C28 + SD rats when compared with control rats (C1-SD, C7-SD, C28-SD). The increase of α-Na^+/K^+-ATPase by SD was diminished in Li-treated rats - Li1-SD vs. Li1 + SD (ns, p > .05), Li7-SD vs. Li7 + SD (ns, p > .05) and C28-SD vs. C28 + SD (ns, p > .05), Fig. 4D,Table 4.

All together, the immunoblot analyses of α-Na^+/K^+-ATPase content in FBC prepared from rats pre-treated with Li for 1-, 7- or 28-days and subsequently exposed to SD indicated that: 1) acute Li treatment of rats (for 1 day) did not significantly alter the α-Na^+/K^+-ATPase level, but the short-term (7 days) and chronic (28 days) Li treatment resulted in decrease of Na^+/K^+-ATPase (Fig. 3A, 4A,Table 4), 2) SD for 3 days enhanced the α-Na^+/K^+-ATPase content in membranes isolated from all Li-untreated samples of FBC (Fig. 3C, 4C Table 4), 3) Li treatment, regardless whether for 1, 7 or 28 days, attenuated the SD-induced increase of α-Na^+/K^+-ATPase protein level (Fig. 3D, 4D,Table 4).

3.4. Regulation of Na^+/K^+-ATPase protein level in hippocampus of rats kept on Li diet for 1, 7 and 28 days and subsequently deprived from sleep for 3 days; immunoblot analysis of α-subunit

Results obtained by immunoblot analysis of α-Na^+/K^+-ATPase in HIP were substantially different from those determined in FBC. The acute (1 day), short-term (7 days) and long-term (28 days) Li treatment did not significantly alter α-Na^+/K^+-ATPase level (Figs. 5A and 6A,Table 4). The same result was found in HIP samples collected from rats which were treated with Li for the same periods of time and subsequently exposed to SD for 3 days (Fig. 5B, 6B,Table 4). However, in conjunction with data obtained in FBC, the deprivation from sleep resulted in an increase of α-Na^+/K^+-ATPase protein level (Fig. 5C, 6C,Table 4) and this increase was not observed in Li-treated rats - Li1-SD vs. Li1 + SD, Li7-SD vs. Li7 + SD and C28-SD vs. C28 + SD, Fig. 5D, 6D,Table 4.

3.5. Regulation of Na^+/K^+-ATPase in forebrain cortex and hippocampus of rats kept on Li diet for 1, 7 and 28 days and subsequently deprived from sleep for 3 days; determination of enzyme activity

Characterization of Na^+/K^+-ATPase by determination of number of

Table 3
2-way ANOVA summary.

Tissue	Parameter	Figures	Tested groups	Factor	F-values(dfn, dfd)
FBC	[^{3}H]ouabain binding	2A	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 32) = 17.00***
				Sleep deprivation	F(1, 32) = 18.76***
				Interaction between both factors	F(1, 32) = 0.33 ns
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 32) = 18.99***
				Sleep deprivation	F(1, 32) = 21.94***
				Interaction between both factors	F(1, 32) = 0.30 ns
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 32) = 25.80***
				Sleep deprivation	F(1, 32) = 16.09***
				Interaction between both factors	F(1, 32) = 0.04 ns
HIPP	[^{3}H]ouabain binding	2B	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 32) = 0.02 ns
				Sleep deprivation	F(1, 32) = 4.07 *
				Interaction between both factors	F(1, 32) = 10.55 **
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 32) = 2.62 ns
				Sleep deprivation	F(1, 32) = 5.36 *
				Interaction between both factors	F(1, 32) = 6.53 **
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 32) = 20.77***
				Sleep deprivation	F(1, 32) = 12.05***
				Interaction between both factors	F(1, 32) = 0.63 ns
FBC	Na^+/K^+-ATPase activity	7A	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 56) = 27.12 ***
				Sleep deprivation	F(1, 56) = 4.12 *
				Interaction between both factors	F(1, 56) = 6.11 *
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 56) = 114.20 ***
				Sleep deprivation	F(1, 56) = 4.09 *
				Interaction between both factors	F(1, 56) = 1.75 ns
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 56) = 22.22 ***
				Sleep deprivation	F(1, 56) = 4.11 *
				Interaction between both factors	F(1, 56) = 6.10 *
HIPP	Na^+/K^+-ATPase activity	7B	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 56) = 251.9 ***
				Sleep deprivation	F(1, 56) = 12.41 **
				Interaction between both factors	F(1, 56) = 20.21 ***
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 56) = 207.8 ***
				Sleep deprivation	F(1, 56) = 5.10 *
				Interaction between both factors	F(1, 56) = 26.76 ***
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 56) = 97.94 ***
				Sleep deprivation	F(1, 56) = 7.33 *
				Interaction between both factors	F(1, 56) = 3.96 ns
FBC	MDA concentration	8A	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 32) = 0.26 ns
				Sleep deprivation	F(1, 32) = 17.60 ***
				Interaction between both factors	F(1, 32) = 1.09 ns
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 32) = 111.60 ***
				Sleep deprivation	F(1, 32) = 14.22 ***
				Interaction between both factors	F(1, 32) = 8.84 **
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 32) = 70.81 ***
				Sleep deprivation	F(1, 32) = 7.28 *
				Interaction between both factors	F(1, 32) = 14.01 ***
HIPP	MDA concentration	8B	C1-SD, Li1-SD, C1 + SD, Li1 + SD	Lithium treatment	F(1, 32) = 14.55 ***
				Sleep deprivation	F(1, 32) = 4.47 *
				Interaction between both factors	F(1, 32) = 15.60 ***
			C7-SD, Li7-SD, C7 + SD, Li7 + SD	Lithium treatment	F(1, 32) = 12.69 ***
				Sleep deprivation	F(1, 32) = 4.44 *
				Interaction between both factors	F(1, 32) = 2.90 ns
			C28-SD, Li28-SD, C28 + SD, Li28 + SD	Lithium treatment	F(1, 32) = 4.47 *
				Sleep deprivation	F(1, 32) = 9.57 **
				Interaction between both factors	F(1, 32) = 5.15 *

The data represent the F-values of a two-way ANOVA of the assays, representing significance as: *, $p < .05$, **, $p < .01$, *** $p < .001$ and ns, $p > .05$; dfn, degrees of freedom numerator, dfd, degrees of freedom denominator.

[^{3}H]ouabain binding sites and α-Na^+/K^+-ATPase protein level was extended and finalized by determination of activity of this enzyme. In both FBC and HIP (Fig. 7A and B,Table 3), the acute (1 day), short-term (7 days) as well as long-term (28 days) treatment of rats with Li resulted in decrease of Na^+/K^+-ATPase activity in all three groups of experimental animals (Li1-SD, Li7-SD, Li28-SD) when compared with corresponding controls (C1-SD, C7-SD, C28-SD). The decrease of Na^+/K^+-ATPase activity by Li was also measured in rats which were pre-treated with Li for 1, 7 or 28 days and subsequently subjected to SD (C1 + SD vs. Li1 + SD; C7 + SD vs. Li7 + SD; C28 + SD vs. Li28 + SD). As before in [^{3}H]ouabain binding and immunoblot assays, SD alone enhanced the Na^+/K^+-ATPase activity. The SD-induced increase of Na^+/K^+-ATPase was diminished in Li-treated rats (Li1-SD vs. Li1 + SD; Li7-SD vs. Li7 + SD; Li28-SD vs. Li28 + SD).

3.6. Inhibitory effect of Li on lipid peroxidation in post-nuclear fractions prepared from forebrain cortex and hippocampus of control and Li-treated rats and after sleep deprivation

The effect of Li treatment on LP proceeding in PNS fractions prepared from FBC and HIP of rats treated with Li for 1, 7 and 28 days was performed by determination of MDA by HPLC. Results presented in Fig. 8A,Table 3 (FBC) indicated that the acute (1 day) Li treatment did not influence MDA production, but PNS fractions prepared from rats treated with Li for 7 or 28 days showed a significant decrease of MDA level. In HIP (Fig. 8B,Table 3), the inhibitory effect of Li on MDA production was not observed.

Importantly, SD of control, Li-untreated rats resulted in an increase of LP when compared with control rats without SD, jointly in FBC and

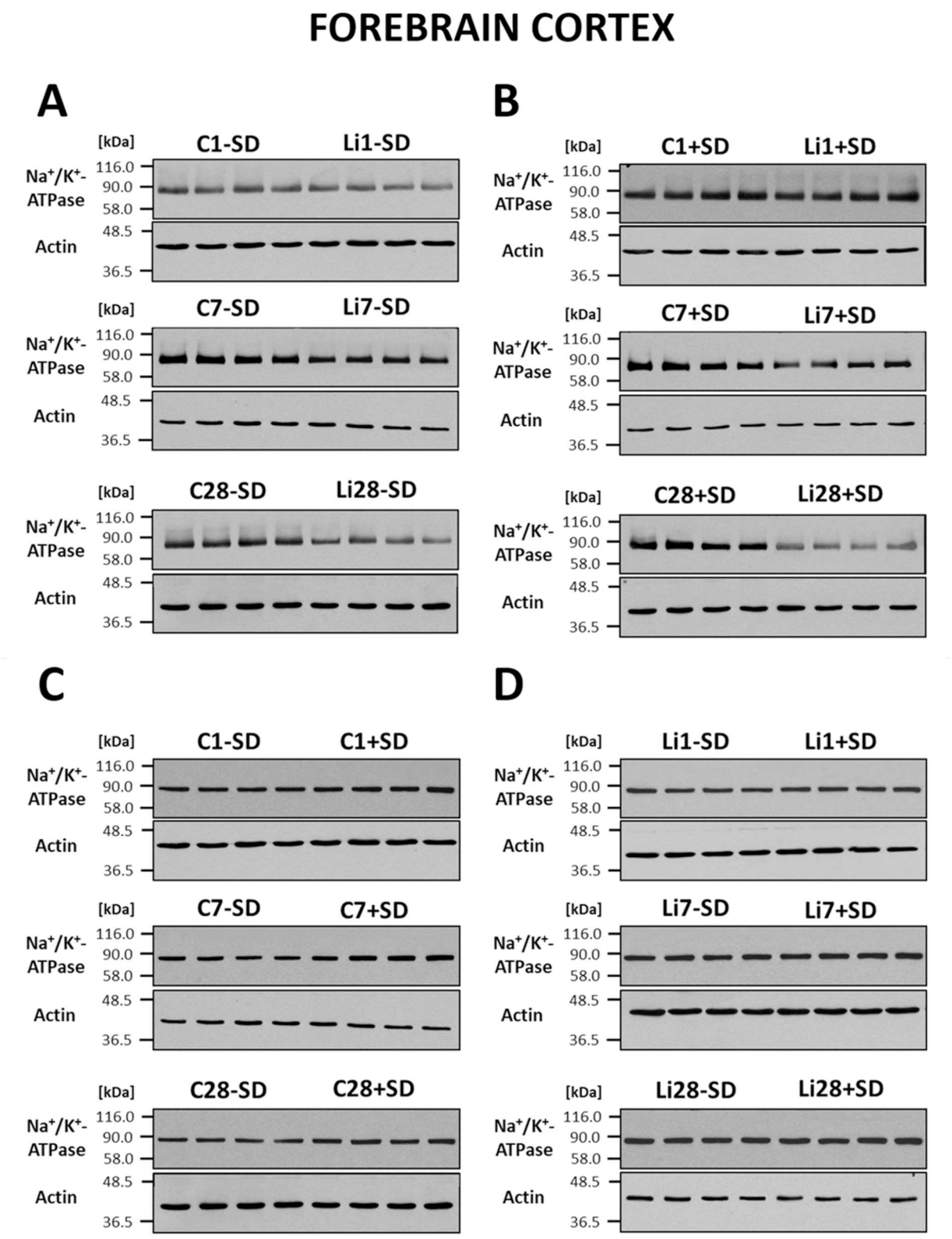

Fig. 3. Typical immunoblots of Na^+/K^+-ATPase and actin in FBC. Frozen aliquots of the same membrane preparations as those used in [^{3}H]ouabain binding experiments (melted only once) were resolved by standard SDS-PAGE and immunoblotted with. α-Na^+/K^+-ATPase Ab. The 20 μg of membrane protein were applied per each lane. The 4 x control (C1-SD, C7-SD, C28-SD; *left*) and 4 x Li-treated (Li1-SD, Li7-SD and Li28-SD; *right*) samples of FBC were run together in the same gel, transferred to the same nitrocellulose sheet and developed (A). (B), C1 + SD vs. Li1 + SD, C7 + SD vs. Li7 + SD and C28 + SD vs. Li28 + SD; (C), C1-SD vs. C1 + SD, C7-SD vs. C7 + SD and C28-SD vs. C28 + SD; (D), Li1-SD vs. Li1 + SD, Li7-SD vs. Li7 + SD, Li28-SD vs. Li28 + SD. Actin was used as a loading control.

HIP and in all experimental groups of rats - C1 + SD vs. C1-SD, C7 + SD vs. C7-SD and C28 + SD vs. C28-SD, Fig. 8A and B**,**Table 3. The SD-induced increase of MDA production was abolished by long-term Li treatment. Thus, treatment of rats with therapeutic Li exhibited the *protective effect* against SD-induced LP proceeding in both FBC and HIP.

Table 4
Student's t-test summary; immunoblot analysis.

Tissue	Figures	Tested groups	t, df
FBC	3A, 4A	C1-SD, Li1-SD	$t = 0.482$; df = 46; ns
		C7-SD, Li7-SD	$t = 2.407$; df = 46; *
		C28-SD, Li28-SD	$t = 2.655$; df = 46; *
	3B, 4B	C1 + SD, Li1 + SD	$t = 0.142$; df = 46; ns
		C7 + SD, Li7 + SD,	$t = 2.185$; df = 46; *
		C28 + SD, Li28 + SD	$t = 3.138$; df = 46; **
	3C, 4C	C1-SD, C1 + SD	$t = 2.366$; df = 46; *
		C7-SD, C7 + SD	$t = 2.865$; df = 46; *
		C28-SD, C28 + SD	$t = 2.164$; df = 46; *
	3D, 4D	Li1-SD, Li1 + SD	$t = 1.235$; df = 46; ns
		Li7-SD, Li7 + SD	$t = 1.529$; df = 46; ns
		Li28-SD, Li28 + SD	$t = 1.610$; df = 46; ns
HIP	5A, 6A	C1-SD, Li1-SD	$t = 0.923$; df = 46; ns
		C7-SD, Li7-SD	$t = 0.863$; df = 46; ns
		C28-SD, Li28-SD	$t = 0.645$; df = 46; ns
	5B, 6B	C1 + SD, Li1 + SD	$t = 0.443$; df = 46; ns
		C7 + SD, Li7 + SD,	$t = 0.978$; df = 46; ns
		C28 + SD, Li28 + SD	$t = 0.758$; df = 46; ns
	5C, 6C	C1-SD, C1 + SD	$t = 3.108$; df = 46; *
		C7-SD, C7 + SD	$t = 3.219$; df = 46; *
		C28-SD, C28 + SD	$t = 3.213$; df = 46; *
	5D, 6D	Li1-SD, Li1 + SD	$t = 0.906$; df = 46; ns
		Li7-SD, Li7 + SD	$t = 1.077$; df = 46; ns
		Li28-SD, Li28 + SD	$t = 1.232$; df = 46; ns

The data represent the t values of a two-tailed unpaired Student's t-test of the assays, representing significance as: *, $p < .05$, **, $p < .01$ and ns, not significant; df, degrees of freedom.

4. Discussion

Among many candidate pathways mediating the Li effect, we decided to test the hypothesis of altered Na^+/K^+-ATPase activity and involvement of peroxidation of membrane lipids in this process. Up-to-now, the effect of *in vivo* administration of therapeutic Li on Na^+/K^+-ATPase activity and [^{3}H]ouabain binding capacity in mammalian brain has not been studied in parallel with the protein level of the enzyme, or in the context of clearly defined time duration of Li-treatment (Clausen et al., 2017; Vosahlikova and Svoboda, 2016). We have also tested whether the stressful state of experimental animals induced by 3-day SD interferes with activity of this enzyme. The SD-induced change of Na^+/K^+-ATPase was determined in Li-untreated rats and compared with rats pre-treated with Li for 1, 7 and 28 days before SD.

The Li concentrations in plasma of all rats on Li-diet was determined by ICP-MS. This analysis (Table 2) showed therapeutic plasma Li concentration in rats on Li-diet and confirmed data of Fukumoto et al. (2001). Noticeably, Li concentration was increased by SD. This result is likely to reflect the disturbance of ionic balance in blood and consequently in brain cells (Brown et al., 2004; Stein, 2002).

The main purpose of our work was to characterise effects of Li and SD on Na^+/K^+-ATPase. In FBC, the application of three independent methods for determination of Na^+/K^+-ATPase converged to the same conclusion – the long term (7 days) and chronic (28 days) treatment of rats with therapeutic Li concentration resulted in decrease of [^{3}H] ouabain binding, protein level of α-subunit and enzyme activity of this crucial enzyme responsible for homeostatic control of intracellular concentrations of Na^+ and K^+ ions (Figs. 2A, 3, 4 and 7A). The acute (1 day) Li exposure was without effect on α-Na^+/K^+-ATPase protein level, but [^{3}H]ouabain binding and enzyme activity was significantly inhibited. The acute effect of Li on these two parameters is surprising since patients need some time to achieve the Li desired effect. One possibility is that Li appears to modulate multiple steps in cellular signalling and that Na^+/K^+-ATPase represents one of the key connection points of these complex regulatory networks (Alda, 2015).

In HIP, the time course and outcome of Li effect on Na^+/K^+-ATPase activity was the same as in FBC - the enzyme activity was decreased in rats treated with Li for 1-, 7- or 28 days (Fig. 7B). The level of α-subunits of Na^+/K^+-ATPase, determined in the same membranes as those used for determination of Na^+/K^+-ATPase activity, was unchanged (Figs. 5, 6). The same result was found in HIP samples collected from rats treated with Li for the same periods of time and subsequently exposed to SD for 3 days. The [^{3}H]ouabain binding was unchanged in HIP of rats exposed to Li diet for 1 and 7 days; the long-term Li-treatment (28 days) resulted in increase of [^{3}H]ouabain binding (Fig. 2B). As our assay medium does not contain sodium and ATP (Svoboda et al., 1988) and [^{3}H]ouabain binding assay used in this work is based on "back-door" phosphorylation of Na^+/K^+-ATPase (Post et al., 1979), this increase may arise as consequence of conformational change of the enzyme molecule (Amler et al., 1987; Sandtner et al., 2011; Teisinger et al., 1988) or multitude of other mechanisms involved in regulation of binding of cardioactive glycosides to this enzyme (Glynn, 2002; Scheiner-Bobis, 2002; Therien and Blostein, 2000).

Our study of Li-untreated, sleep-deprived rats produced consistent and new findings. Membranes prepared from both FBC and HIP exhibited an increased [^{3}H]ouabain binding, higher α-Na^+/K^+-ATPase protein level and higher enzyme activity than those prepared from SD-unexposed rats (Figs. 2–7). The Li pre-treatment, regardless whether for 1, 7 or 28 days, attenuated this SD-induced increase of Na^+/K^+-ATPase.

Evidence for up-regulation of the number of [^{3}H]ouabain binding sites, α-subunit level and Na^+/K^+-ATPase activity by stress alone is original finding not reported in the literature. If the deprivation from sleep for 3 days, as an experimental approach to mimic the manic phase of BD, results in up-regulation of Na^+/K^+-ATPase, then the inhibitory effect of prolonged Li may be seen as a pharmacological compensation to reverse the stress-induced shift and return the Na^+/K^+-ATPase back to control level.

This interpretation is compatible with RNA-sequencing analysis of gene expression in hyper-excitable hippocampal neurons derived from Li-responsive BD patients. Transcription of mitochondrial genes in such neurons was significantly down-regulated, but transcription of the Na^+/K^+-ATPase pathway gene NKAIN was up-regulated 2.5-fold (Mertens et al., 2015). The hyper-excitability phenotype was selectively reversed by Li in neurons derived from patients who responded to Li treatment, but not in neurons prepared from non-responsive patients. So, the up-regulation of Na^+/K^+-ATPase in FBC and HIP of sleep-deprived rats might be regarded as compensatory adjustment in stressed animals.

In the last part of our work we tested the intensity of LP proceeding in PNS fractions prepared from FBC and HIP of all groups of experimental animals (Fig. 8). The acute Li treatment did not influence MDA production in both parts of brain, PNS fractions prepared from rats treated with Li for 7 or 28 days showed a significant *decrease* of MDA concentrations only in FBC. SD in Li-untreated rats resulted in an *increased* production of MDA, jointly in FBC and HIP - C1 + SD vs. C1-SD, C7 + SD vs. C7-SD and C28 + SD vs. C28-SD. The SD-induced increase of MDA was abolished by Li pre-treatment. We could therefore conclude that treatment of rats with therapeutic Li exhibited the *protective effect* against SD-induced LP proceeding in FBC and HIP.

The mood stabilizing agents, Li and valproate were found to exert strong antioxidant effects in brain tissues of experimental animals (Shao et al., 2005) as well as in erythrocytes collected from Li-treated BP patients (Banerjee et al., 2012; Rodrigo et al., 2007). As the contemporary view on biochemical aetiology of BD suggests that oxidative stress plays an important role in the pathophysiology of BD (for reviews see Joshi and Praticò (2014), Kim et al. (2017), Pandya et al. (2013), Viswanath et al. (2015)), our results indicating the increased concentration of MDA in FBC of stressed animals and anti-oxidant potency of Li are fully compatible with this view. The intra-cerebral application of ouabain was associated with the appearance of mania-like behaviour and induction of oxidative stress (Riegel et al., 2010).

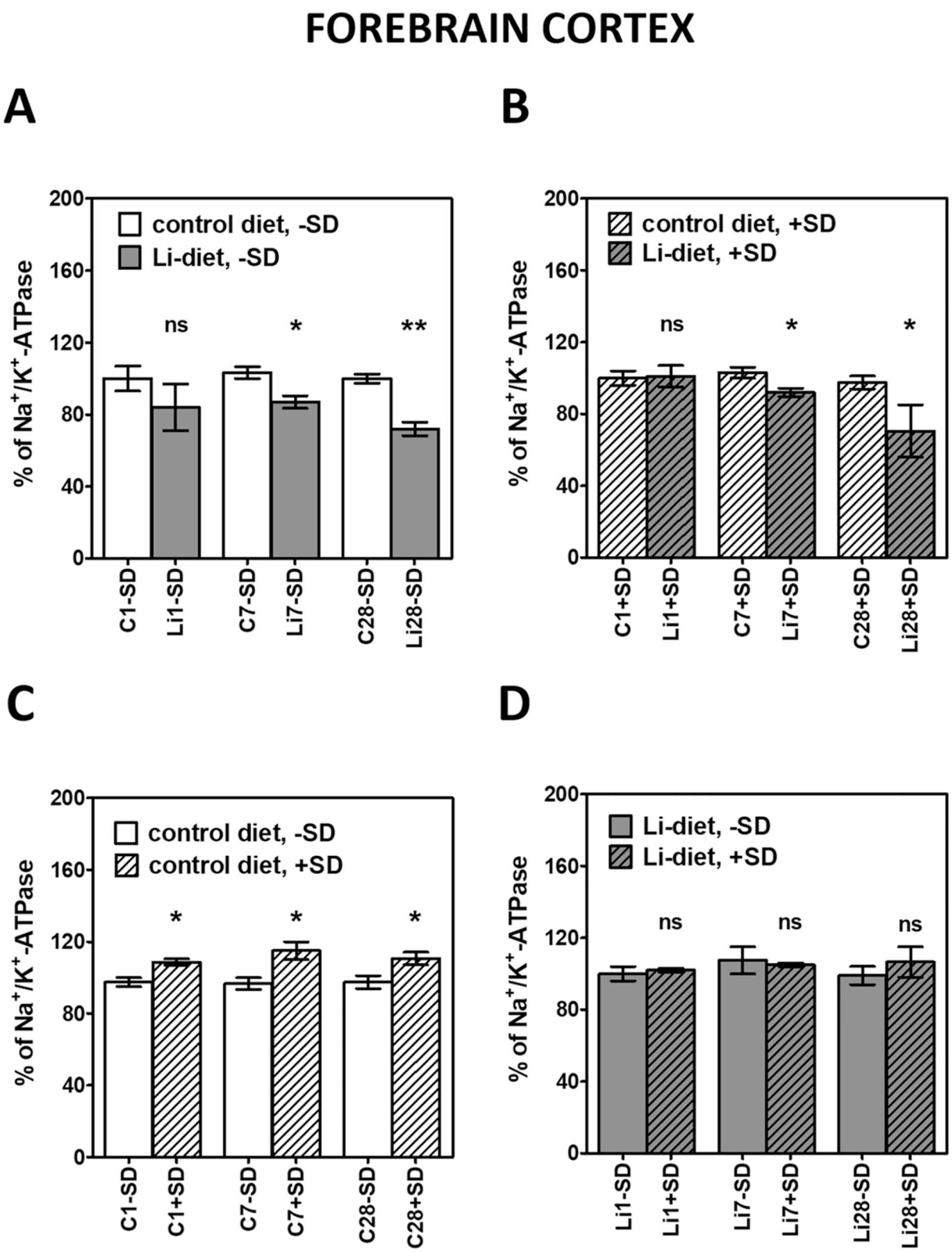

Fig. 4. Na^+/K^+-ATPase protein level in membranes prepared from forebrain cortex of control rats and rats treated with therapeutic Li concentration for 1, 7 and 28 days followed by deprivation from sleep for 3 days on control or Li diet; *immunoblot analysis of α-subunit of Na^+/K^+-ATPase*. The same legend as in Fig. 3. Statistical analysis was based on six blots, i.e. comparison of totally 24 (6 × 4) vs. 24 (6 × 4) immunoblot signals of Na^+/K^+-ATPase determined in FBC from each group of experimental animals. The data represent the means ± SEM expressed as % of control values, 100% and were analysed by Student's *t*-test. *, $p < .05$; ns, $p > .05$.

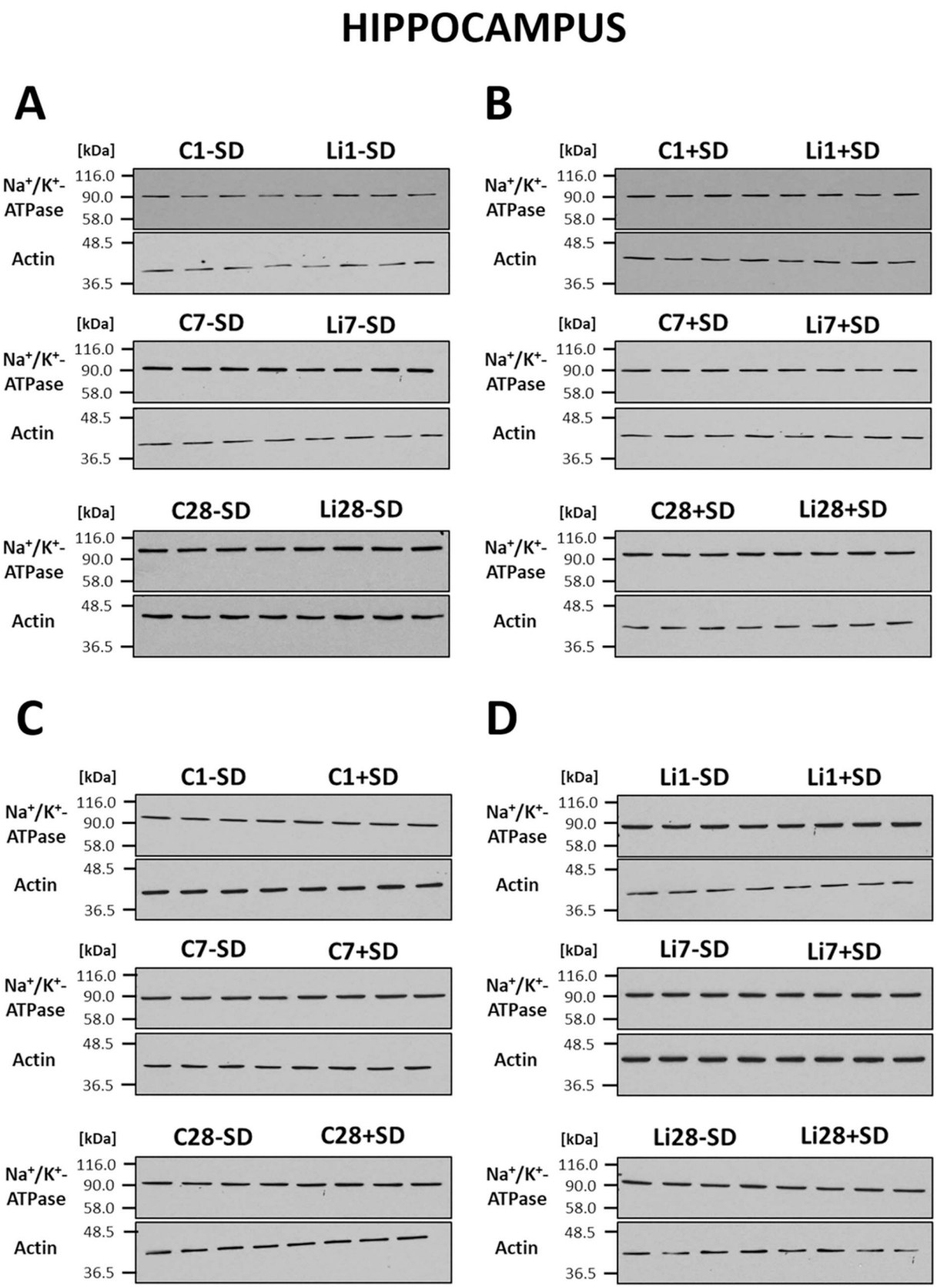

Fig. 5. Typical immunoblots of Na^+/K^+-ATPase and actin in hippocampus. Frozen aliquots of the same membrane preparations as those used in [^{3}H]ouabain binding experiments (melted only once) were resolved by standard SDS-PAGE and immunoblotted with α-Na^+/K^+-ATPase Ab. The 20 μg of membrane protein were applied per each lane. The 4 x control (C1-SD, C7-SD, C28-SD; *left*) and 4 x Li-treated (Li1-SD, Li7-SD and Li28-SD; *right*) samples of HIP were run together in the same gel, transferred to the same nitrocellulose sheet and developed (A). (B), C1 + SD vs. Li1 + SD, C7 + SD vs. Li7 + SD and C28 + SD vs. Li28 + SD; (C), C1-SD vs. C1 + SD, C7-SD vs. C7 + SD and C28-SD vs. C28 + SD; (**D**), Li1-SD vs. Li1 + SD, Li7-SD vs. Li7 + SD, Li28-SD vs. Li28 + SD. Actin was used as a loading control.

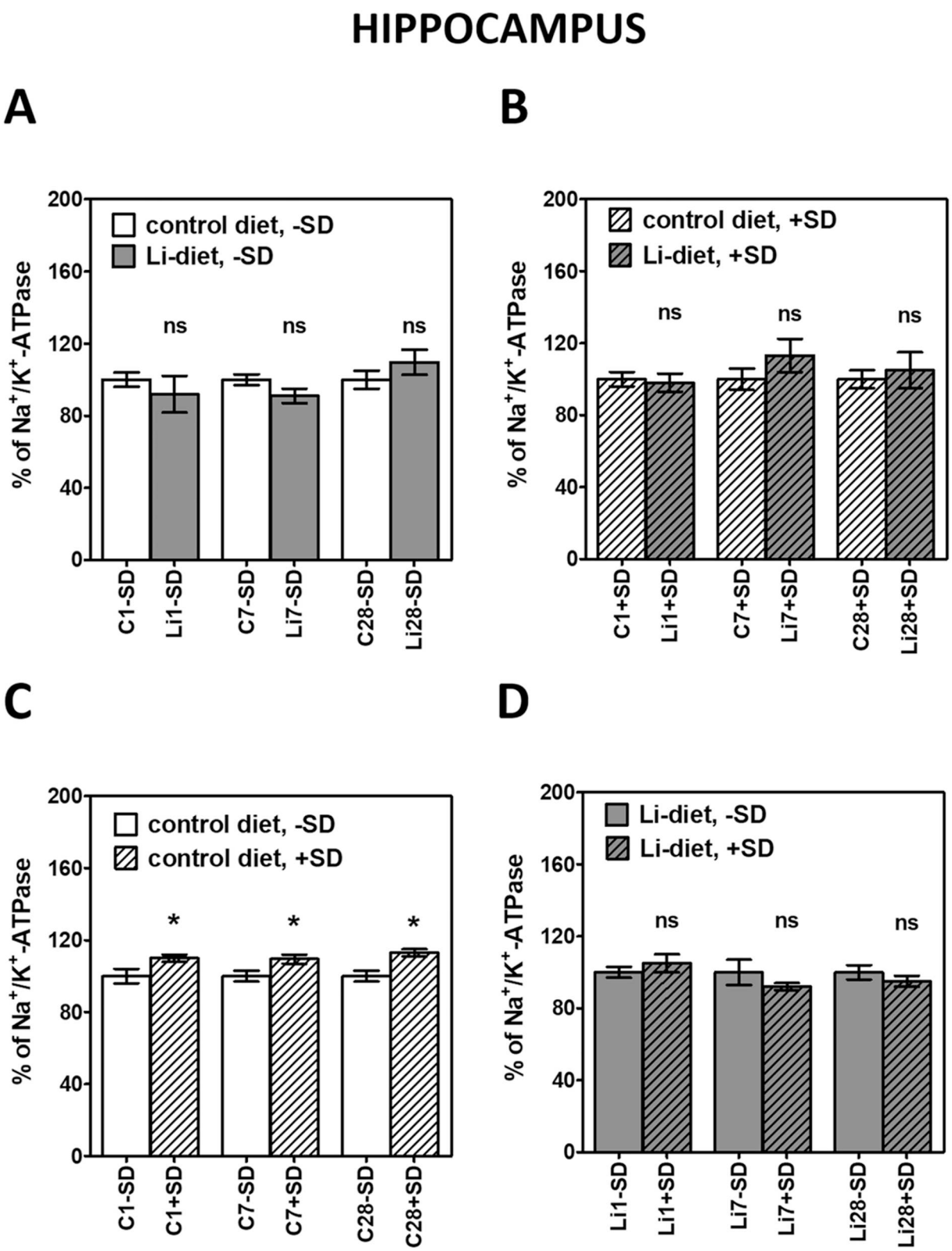

Fig. 6. Na^+/K^+-ATPase protein level in membranes prepared from hippocampus of control rats and rats treated with therapeutic Li concentration for 1, 7 and 28 days followed by 3-day sleep deprivation on control or Li diet; *immunoblot analysis of α-subunit of Na^+/K^+-ATPase*. The same legend as in Fig. 5. Statistical analysis was based on six blots, i.e. comparison of totally 24 (6 × 4) vs. 24 (6 × 4) immunoblot signals of Na^+/K^+-ATPase determined in HIP from each group of experimental animals. The data represent the means ± SEM expressed as % of control values, 100% and were analysed by Student's *t*-test. *, $p < .05$; ns, $p > .05$.

Besides regulation of Na^+/K^+-ATPase synthesis by thyroid hormones, mineralocorticoids, glucocorticoids, progesterone, prostaglandin E1, insulin and numerous growth factors (Borsick et al., 2006; Celsi and Wang, 1993; Li and Langhans, 2015; Lo and Klein, 1992), catecholamines were reported to increase Na^+/K^+-ATPase activity in rat brain subcellular fractions under *in vitro* conditions (Gilbert et al.,

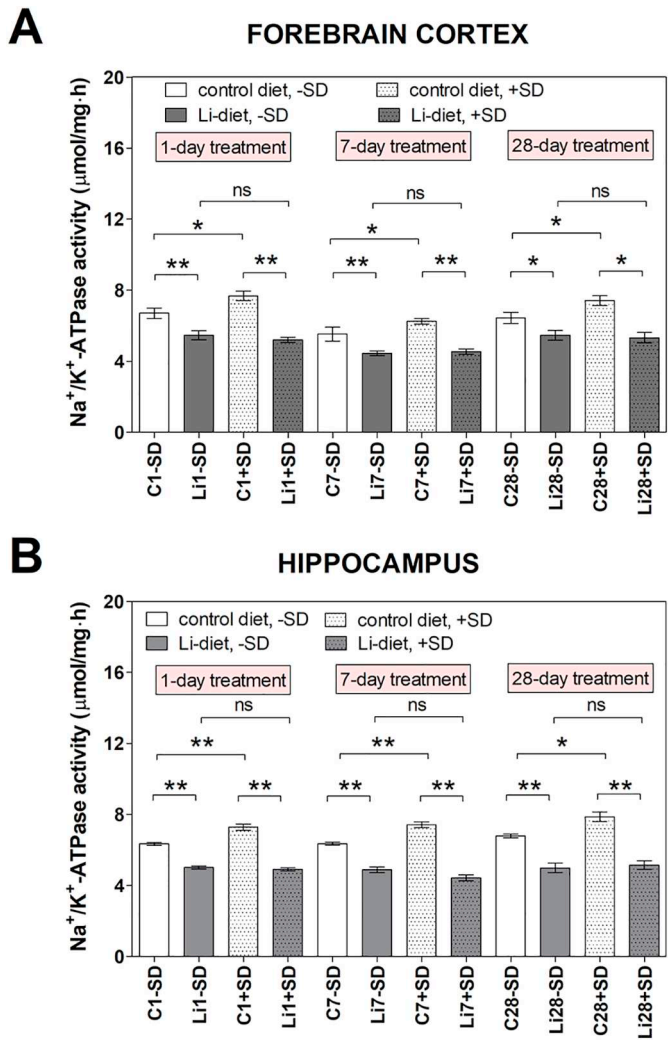

Fig. 7. Na^+/K^+-ATPase activity in membranes prepared from forebrain cortex (A) and hippocampus (B) of control rats and rats treated with therapeutic Li concentration for 1, 7 and 28 days followed by 3 days of sleep deprivation. Na^+/K^+-ATPase activity was measured as described in Methods. Measurement of each membrane preparation was carried out in three independent membrane preparations in triplicates in each and Na^+/K^+-ATPase activity expressed as μmol P_i/h × mg of protein. The data represent the means ± SEM. Pairwise comparison: *, $p < .05$; **, $p < .01$; ns, $p > .05$.

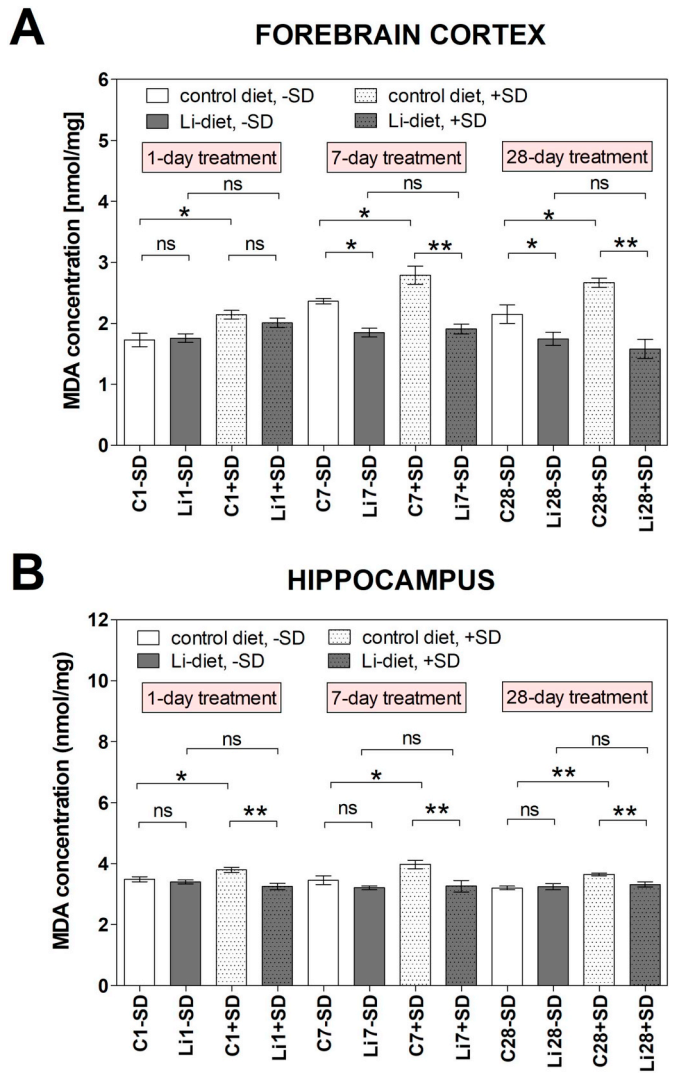

Fig. 8. MDA concentration in PNS fractions prepared from forebrain cortex (A) and hippocampus (B) of control rats and rats treated with therapeutic Li concentration for 1, 7 and 28 days followed by 3 days of sleep deprivation. Determination of MDA in each group of experimental animals was performed in three independent membrane preparations in triplicates in each. The numbers represent the means ± SEM of MDA concentration expressed as nmol/mg protein. Pairwise comparison: *, p < .05; **, p < .01; ns, p > .05.

1975; Godfraind et al., 1974; Lee and Phillis, 1977; Schaefer et al., 1974; Schaefer et al., 1972; Wu and Phillis, 1978; Yoshimura, 1973). This result was interpreted as consequence of suppression of inhibition of Na^+/K^+-ATPase by calcium ions (Godfraind et al., 1974; Hexum, 1977), protection against inhibition by ascorbic acid (ASC) present in cytosol fraction (Schaefer et al., 1974; Schaefer et al., 1972) or mediated by specific alpha- and beta-adrenergic receptors (Wu and Phillis, 1979). Stimulation of rat brain Na^+/K^+-ATPase by norepinephrine via adrenergic receptors was also reported under *in vivo* conditions (Swann, 1983; Swann et al., 1981a; Swann et al., 1981b).

Studies of Svoboda and Mosinger (1981a, 1981b) showed that the effect of norepinephrine and epinephrine on Na^+/K^+-ATPase and LP was not mediated by specific α- or β-adrenergic receptors. The crucial part of catecholamine molecule was represented by orto-catechol structure which is able to chelate the ferrous or calcium ions. We have also tested the effect vanadium compounds (Svoboda et al., 1984a, 1984b). Both forms of vanadium inhibited Na^+/K^+-ATPase activity - EC_{50} values were 0.3 μM and 1 μM for vanadate (VO_3^-) and vanadyl (VO^{2+}), respectively.

The mechanism of action of catecholamines on brain Na^+/K^+-ATPase was intensively studied since those old days and, in relevance to our results indicating the SD-induced increase of Na^+/K^+-ATPase in Li-untreated rats, studies of Gulyani and Mallick (1993), Mallick and Adya (1999), Majumdar et al. (2003) and Mallick et al. (2010) showed that after REM sleep loss, the Na^+/K^+-ATPase activity was increased in the whole brain as well as in synaptosomal membranes. The increase was paralleled by an increase of norepinephrine level and interpreted as α1-adrenergic stimulation mediated by PLC and intracellular Ca^{2+}. The LP estimated as TBARS was decreased (Das et al., 2008), in the contrary to majority of literature data, which indicated the increased LP in the whole brain, cerebral cortex or hippocampus of rats subjected to deprivation from REM sleep (Villafuerte et al., 2015). The increased LP in cortex and hippocampus of rats exposed to SD for 3 days was also reported by Khadrawy et al. (2011), however, the increased LP was accompanied by decrease of Na^+/K^+-ATPase activity.

When considering the reasons why the experimental results and mechanisms suggested to play a role in stress-induced alteration of LP and Na^+/K^+-ATPase activity are so much heterogeneous, we suggest

that this variability may be caused, besides multitude of other factors (for reviews Can et al. (2014), Joshi and Praticò (2014)), by an interplay among ASC and intracellular iron and calcium ions. The ASC concentrations in the brain are in mM range (Du et al., 2012; Hornig, 1974, 1975; Levin, 1974; Rajalakshmi and Patel, 1968). At these concentrations, ASC chelates ions and acts as an endogenous antioxidant. However, in the presence of transitional metal ions, ASC can also exert pro-oxidant effects (Svoboda and Mosinger, 1981a; Svoboda et al., 1984a). As suggested by Du et al. (2012), the pro-oxidant effects of ASC may be important *in vivo* depending on the availability of catalytic metal ions. In healthy individuals, iron is largely sequestered by iron binding proteins such as transferrin and ferritin (Richardson and Ponka, 1997; Wang et al., 2010).

The peroxidation of rat brain Na^+/K^+-ATPase by H_2O_2, Fe^{2+} and ASC was described to cause an irreversible inhibition Na^+/K^+-ATPase activity combined with degradation of native protein structure of α/β subunits by proteasomal and endosomal/lysosomal proteolytic enzymes (Huang et al., 1992, 1994; Zolotarjova et al., 1994). To avoid hydrolytic degradation of Na^+/K^+-ATPase, in our experiments, rat brain FBC and HIP were homogenized in the presence of fresh 1 mM PMSF added before the onset of homogenization; membrane isolation was carried out in Ca^{2+}-free medium containing 1 mM EDTA and the final membrane sediment was suspended in 50 mM Tris-HCl, 1 mM EDTA (pH 7.6), frozen in liquid nitrogen, stored at −80 °C and used only once (see Methods).

Further, to avoid eventual artefacts generated in the complex biological samples when using TBARS method for detection of LP (Forman et al., 2015), in our experiments, MDA concentration in PNS fractions prepared from FBC and HIP was determined by HPLC. The PNS fractions were snap frozen in liquid nitrogen immediately after preparation, stored at −80 °C and used only once. The diversity of results may be also caused by different response of neurons and glial cells as the REM SD-induced increase of noradrenaline was found to stimulate neuronal but inhibit the glial Na^+/K^+-ATPase in rat brain (Baskey et al., 2009).

Thus, if our data indicating the SD-induced increase of MDA level in Li-untreated rats are relevant to clinical situation, patients undergoing the manic phase of BD should exhibit the increased level of LP. In agreement with this idea, TBARS were significantly higher in blood and plasma of manic patients when compared with controls, euthymic, depressed and schizophrenic patients (Andreazza et al., 2008; Kunz et al., 2008; Machado-Vieira et al., 2007). In depressive period of BD, plasma level of TBARS was unchanged (de Sousa et al., 2014). Evidence for increased plasma level of TBARS in all stages of BP disease (early- and late-stage, mania/hypo-mania and depression) was brought by Siwek et al. (2016). Accordingly, the serum TBARS were increased in BP patients compared to age and sex matched healthy controls. The same trend was observed in the BP patients stabilized on Li therapy compared to the Li naive ones (Banerjee et al., 2012). In animal models, the review of current experimental evidence ended up with conclusion that SD promotes oxidative stress (Villafuerte et al., 2015).

The increased (Akagawa et al., 1980; Antia et al., 1992, 1995), decreased (Banerjee et al., 2012; Hokin-Neaverson and Jefferson, 1989; Hokin-Neaverson et al., 1974; Naylor et al., 1980; Scott and Reading, 1978) or unchanged (Hesketh et al., 1977; Thakar et al., 1985) Na^+/K^+-ATPase activity was found in erythrocytes of BP patients. Meta-analysis of erythrocyte Na^+/K^+-ATPase activity in BD suggested a significant mood-state-related decrease of Na^+/K^+-ATPase activity in both manic and BP depressed patients when compared to euthymic BP patients, but not when BP patients were compared to normal controls. The overall change of Na^+/K^+-ATPase activity was small or moderate in magnitude (Looney, and el-Mallakh, R.S., 1997).

Measurement of activity of Na^+/K^+-pump as transport of rubidium from plasma to erythrocytes after the oral administration of rubidium chloride indicated the increased Na^+/K^+-ATPase activity *in vivo* in unmedicated patients with acute manic illness (Wood et al., 1989a). The increase was noticed when manic BP patients were compared with matched healthy volunteers. On the other hand, the rate of rubidium uptake into erythrocytes prepared from the euthymic, Li-treated patients was lower than in a matched group of un-medicated manic patients (Wood et al., 1989b). Oral administration of Li to healthy volunteers resulted in an increased rate of rubidium uptake into erythrocytes, suggesting a direct stimulation of Na^+/K^+-ATPase activity by Li (Wood et al., 1989c).

In nucleated cells, such as HeLa cells, Na^+/K^+-ATPase activity undergoes adaptation to increase of intracellular sodium and this ability to adapt was shown as an increase in number of [^{3}H]ouabain binding sites in membranes or up-regulation of functional activity of this enzyme in cells (Boardman et al., 1975; Boardman et al., 1972; Pollack et al., 1981). Methods used to increase the cell sodium were incubation either with ethacrynic acid or in a medium with low potassium concentration. The lymphocytes of manic depressive patients had a significantly reduced ability to produce new pump sites measured as number of [^{3}H]ouabain binding sites when compared with healthy controls (Naylor and Smith, 1981). The incubation of lymphocytes prepared from healthy subjects in Li (8 mM) or ethacrynic acid (1 μM) resulted in time-dependent up-regulation of Na^+/K^+-ATPase activity evidenced as the increase in number of [^{3}H]ouabain binding sites in membranes (Wood et al., 1991). However, this adaptive up-regulation was absent in lymphocytes isolated from euthymic drug-free patients with a history of manic depressive psychosis. It was also missing in lymphocytes of euthymic patients taking Li.

As mentioned above, the activity and expression level of Na^+/K^+-ATPase were increased in rat brain after deprivation from REM sleep (Gulyani and Mallick, 1993; Majumdar et al., 2003; Mallick and Adya, 1999; Mallick et al., 2010). These data are in line with results presented in this work which indicate the SD-induced increase of [^{3}H]ouabain binding, Na^+/K^+-ATPase protein level as well as Na^+/K^+-ATPase activity in repeatedly washed membranes prepared from FBC and HIP of Li-untreated rats. The increase of Na^+/K^+-ATPase was in our case accompanied by enhanced LP (determined as production of MDA by HPLC), whilst the data of Das et al. (2008) showed the decreased LP estimated as TBARS. Our measurements agree with majority of literature data, which indicated the increased LP in the whole brain, cerebral cortex or hippocampus of rats subjected to deprivation from REM sleep (for review Villafuerte et al. (2015)). The increased LP in cortex and hippocampus of rats exposed to SD for 3 days was also reported by Khadrawy et al. (2011), however, the increased LP was accompanied by decrease of Na^+/K^+-ATPase activity.

5. Conclusions

The acute (1 day), short-term (7 days) as well as chronic (28 days) treatment of rats with therapeutic Li concentration *in vivo* resulted in a decrease of Na^+/K^+-ATPase activity in membranes isolated from FBC and HIP of these animals.

In Li-untreated rats, deprivation from sleep for 3 days resulted in increase of Na^+/K^+-ATPase activity in both FBC and HIP; this increase was attenuated in Li-treated animals.

The up-regulation of Na^+/K^+-ATPase activity by SD was paralleled by an increased LP determined as production of MDA in post-nuclear fraction. The SD-induced increment of MDA production was diminished in Li-treated rats.

We conclude that SD alone up-regulates Na^+/K^+-ATPase together with increased peroxidative damage of lipids. Chronic treatment of rats with Li before SD, protects the brain tissue against this type of damage and decreases Na^+/K^+-ATPase level back to control level.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the Czech Science Foundation GA CR (GA17-07070S), from the institutional project of the Institute of Physiology of the Czech Academy of Sciences (RVO:67985823) and from the institutional research plan of Institute of Analytical Chemistry of the Czech Academy of Sciences (RVO:68081715).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2020.109953.

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