RESEARCH PAPER

Acta Neurobiol Exp 2022, 82: 245–253
DOI: 10.55782/ane-2022-023

Differential expression profile between amygdala and blood during chronic lithium treatment in a rat model of depression – a pilot study

Kosma Sakrajda[1]*, Dawid Szczepankiewicz[2], Joanna Nowakowska[1], Piotr Celichowski[3], Ewa Banach[4], Przemysław Zakowicz[5], Paweł Kołodziejski[2], Ewa Pruszyńska-Oszmałek[2], Joanna Pawlak[5†], Aleksandra Szczepankiewicz[1†]

[1] Molecular and Cell Biology Unit, Poznan University of Medical Sciences, Poznan, Poland,
[2] Department of Animal Physiology, Biochemistry and Biostructure, Poznan University of Life Sciences, Poznan, Poland,
[3] Department of Histology and Embryology, Poznan University of Medical Sciences, Poznan, Poland,
[4] Laboratory of Electrophysiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland,
[5] Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland,
[†] Equally contributed senior authors,
** Email: kosma.sakrajda@gmail.com*

Lithium is a mood stabilizer widely used in the pharmacotherapy of bipolar disorder and treatment-resistant depression. Taking into account dysregulated inflammatory activity in depression and the immunomodulatory role of lithium, we hypothesized that genes associated with inflammatory responses may be potential biomarkers of lithium action. We aimed to compare gene expression changes between the brain and the periphery after chronic lithium administration in an animal model of depression. Depressive behavior was induced by chronic mild stress protocol for 4 weeks. After 2 weeks, rats started to receive lithium (study group) or water (reference group). The control group were rats not exposed to stress. Amygdala, hippocampus, frontal cortex and peripheral blood were analyzed using whole transcriptome expression microarrays. Changes were confirmed with qPCR and ELISA assay. After 2 weeks of lithium administration, we observed significant changes in gene expression between amygdala and peripheral blood. Logistic regression analysis determined *Alox15* expression as a predictor of lithium status, as its expression was tissue-specific and increased in amygdala and decreased in blood. Analysis of serum ALOX15 protein revealed its upregulation after two-week lithium administration. Our study suggests that lithium may have therapeutic potential in depressive behaviors. These results indicate immunomodulatory effect of lithium and that *Alox15* may be a new potential marker of chronic lithium treatment.

Key words: depressive disorder, animal model, lithium, gene expression, *Alox15*

INTRODUCTION

Depressive disorders are psychiatric conditions affecting mood, daily functioning and motivation. Major depressive disorder (MDD) is characterized by depressed mood, decreased energy, anhedonia, problems with concentration, and suicidal thoughts and attempts in its most severe form (James et al., 2018). Previous high-throughput molecular studies and meta-analyses highlighted the contribution of disturbances in the central nervous system i.e., neurotransmission, synaptic structure and neurotrophic pathways, hypothalamic-pituitary-adrenal (HPA) stress axis dysregulation. Furthermore, there are alterations less specific to the brain such as olfactory

Received 9 January 2022, accepted 5 May 2022

transduction pathways and immune system activation including microglia polarization, proinflammatory cytokine production and metabolic changes (Szczepankiewicz et al., 2013; 2021b; Kohli et al., 2016; Malhi and Mann, 2018; Enache et al., 2019; Howard et al., 2019; Penner-Goeke and Binder, 2019; Sakrajda and Szczepankiewicz, 2021).

Lithium has been well described in treating mainly bipolar disorder, but previous studies also indicated its therapeutic potential to treat depression (Maletic and Raison, 2014; Rybakowski, 2020), in particular treatment-resistant depression and high suicidal risk patients (Abou-Saleh et al., 2017; Undurraga et al., 2019; Rybakowski, 2020). Studies focused on molecular action of lithium described its impact on the glycogen synthase kinase 3 beta (GSK-3β) inhibition, the phosphatidylinositol pathway, and cyclic adenosine monophosphate (cAMP) second messenger signaling pathway (Bellivier and Marie-Claire, 2018; Rybakowski, 2020). Furthermore, lithium also showed immunomodulatory potential and, in addition to the brain, the immune system is significantly involved in lithium responsiveness (Krebs et al., 2020; Najafi et al., 2020). Recently, we found that lithium influences olfactory and taste transduction gene expression pathways in rat models of mania and depression (Szczepankiewicz et al., 2021a).

So far, a few studies described changes in the brain transcriptome upon lithium treatment (McQuillin et al., 2007; Chetcuti et al., 2008; Brzózka et al., 2016). However, only the latter study analyzed the effect of lithium in the hippocampus of animals undergoing a stress protocol, although the lithium was applied before the stress procedure. Moreover, despite studies comparing the central and peripheral gene expression changes (Berrettini et al., 1983; Leschiner et al., 2000; Li et al., 2012) there is still a lack of studies comparing the gene expression profile between distinct brain regions and peripheral blood after lithium treatment in a depression model. Therefore, we hypothesized that lithium affects the gene expression profile in selected brain regions, and that these changes correspond to those observed in peripheral blood. The genes altered by lithium both in the brain and periphery may be useful biomarkers of lithium action in depression.

Therefore, this study aimed to analyze the gene expression profile after chronic lithium administration in three brain regions involved in mood regulation (amygdala, frontal cortex and hippocampus) and in peripheral blood in a rat model of depression. The study also aimed to identify genes showing significant differences between brain and blood as they may be new potential biomarkers of lithium action.

METHODS

Animal model of depression

The local ethical committee approved the animal-based experimental procedures (University of Life Sciences, agreement no. 22/2017, 23 June 2017), and the study was carried out according to the 3Rs rule. We used adult male Wistar rats with the baseline weight of 180 ± 10 g (outbred, Crl: Wl, AnimaLab, Poland). The rats were group-housed and kept for a week of acclimatization with food and water availability *ad libitum*, 12 h light/dark cycle and a temperature of 22 ± 1°C, before random division into three experimental groups (chronic mild stress-exposed group receiving lithium, chronic mild stress-exposed group receiving water and a control group not exposed to stress) with three animals in each group. The depressive behavior was obtained using the chronic mild stress protocol (CMS) as described previously (Papp, 2012; Szczepankiewicz et al., 2021a; 2021b). The control group was maintained under the same conditions as the other experimental groups. The depressive-like behavior was assessed during the light phase of the cycle using forced swim test (FST) and open field test (OFT). Change in the analyzed parameters of greater than 40% after CMS protocol was considered as confirmation of depressive-like behavior, as described previously (Szczepankiewicz et al., 2021a; 2021b).

Lithium administration

After two weeks of the CMS protocol, lithium was administered to the lithium-receiving group of animals exposed to stress. Lithium solution in water was given daily directly into the mouth with a syringe for two weeks in the dose of 1 mg/kg of body mass (Atcha et al., 2010; Perveen et al., 2013; Szczepankiewicz et al., 2021a). The non-lithium treated group exposed to stress, as well as the control group received water in the same manner.

Tissue collection

Two weeks after the first dose of lithium or water, rats were sacrificed by decapitation. The brain tissue regions (amygdala, hippocampus and frontal cortex) and blood were collected immediately after the animals were sacrificed. Brain regions were extracted and cleaned from white matter and subcortical structures, then snap-frozen in liquid nitrogen and stored in -80°C for further analysis. Peripheral blood samples were

collected in EDTA coated anticoagulant tubes and tubes without anticoagulant for RNA extraction and serum protein levels analysis. The EDTA tubes with the addition of lysis buffer were stored at -80°C for further RNA extraction. The tubes without anticoagulant were centrifuged after one hour to obtain serum, and the serum samples were frozen at -80°C for further analysis.

Microarray gene expression analysis

The brain and blood samples for RNA extraction were used to assess the gene expression profile. RNA from brain regions was extracted using Nucleospin RNA/Protein kit (Macherey Nagel, Dylan, Germany) and from the blood using a Nucleospin RNA Blood kit (Macherey Nagel, Dylan, Germany). RNA integrity (RIN) was assessed using Tape Station 2200 (Agilent Technologies, Cedar Creek, TX, USA). RNA concentration was measured using a fluorimeter (Quantus, Promega, Madison, WI, USA). The RNA samples from the amygdala, hippocampus, frontal cortex and blood from all animals were used for microarray analysis in the input amount of 100 ng. We conducted microarray transcriptome profiling using SurePrint G3 Rat Gene Expression v2 Microarray Kit in the format 8 × 60 k and one-color Low Input Quick Amp Labeling Kit (Agilent) following the manufacturer's protocol. The hybridization signals were detected using SureScan Dx Microarray Scanner (Agilent) and analyzed with Agilent Feature extraction software v.12.0.3.1.

qPCR gene expression analysis

For qPCR verification, 100 ng of total RNA samples was used for reverse transcription using Go Script Reverse Transcription Kit (Promega) following the manufacturer's protocol. The qPCR with SYBRGreen and specific primers of our own design (Table 1) were used to assess the mRNA expression of selected genes.

We used *Gapdh* as an endogenous control for brain samples and *Actb* for peripheral blood samples, based on a pilot optimization experiment (data not shown). The amplification and detection were performed using the Abi Prism 7900HT detection system (Applied Biosystem). The expression levels were assessed using the -ΔΔCt method.

Protein expression in rat serum

For the *Alox15* gene, expression at the protein level was analyzed in the serum from stress-exposed rats receiving lithium as compared to the non-lithium treated stress-exposed group. Concentrations of ALOX15 protein in serum was measured using Abbexa Rat Arachidonate 15-Lipoxygenase (ALOX15) ELISA kit following the manufacturer protocol. Samples were run in technical duplicates. The absorbance was read on a plate reader (Asys UVM 340) at wavelength 450 nm. Protein concentration was then quantified against a standard curve. The detection range of the kit was 31.2 – 2000 pg/ml.

Statistical analysis

Results of behavioral testing were analyzed using a t-test for paired samples ($p<0.05$) after performing the Shapiro-Wilk test to verify the normality of data distribution in Statistica 14.0 software (from StatSoft, TIBCO Software Inc.).

The analysis of gene expression data from microarray analysis was performed using Gene Spring 14.9 software (from Agilent Technologies, Santa Clara, CA, USA). We identified differentially expressed genes based on a fold of change (FC) calculation, using moderated t-statistics from the empirical Bayes method after normalization of fluorescence signal. The list of significant changes in expressed transcripts ($P<0.05$ and $FC>1.5$) was generated using filtering (moderated t-test with FDR multiple test correction).

Venn diagrams presenting the shared significantly changed genes between brain regions and blood were prepared using a free-to-use tool http://bioinformatics.psb.ugent.be/webtools/Venn.

We used logistic regression to estimate if expression of selected genes depending on tissue (brain or blood)

Table 1. Primer sequences for gene expression analysis.

Gene	Forward primer	Reverse primer
Gapdh	CAACTCCCTCAAGATTGTCAGCAA	GGCATGGACTGTGGTCATGC
Actb	GCAGGAGTACGATGAGTCCG	ACGCAGCTCAGTAACAGTCC
Alox15	ACCTCCCTGTAGACCAACGA	GGCCACTCTTGAAAACGCAG

can be a good predictor of lithium treatment status (p<0.05), based on normalized signal values. To compare the differences in the *Alox15* mRNA expression and the protein level between groups, we used a t-test (p<0.05) after verifying the normal distribution of data with the Shapiro-Wilk test. Analyses were performed in Statistica 14.0 software (from StatSoft, TIBCO Software Inc.).

RESULTS

Behavioral changes after lithium administration

After 4-week CMS protocol, the depressive-like behavior manifested by reduced exploration time and distance in OFT and shorter active climbing time in FST compared to the control group (non-stress-exposed rats) (Szczepankiewicz et al., 2021b). The two-week lithium administration resulted in behavioral changes in lithium-treated rats compared to the non-treated depression group. The lithium-treated group did not differ significantly compared to the control group. After two-week lithium treatment, the stress-exposed rats presented significantly reduced immobility time (t=-4.075, P=0.015), longer exploration time (t=2.780, P=0.049), and a higher medium speed and longer distance travelled (t=3.806, P=0.019 and t=3.790 P=0.019, respectively, shown in Fig.1A) in OFT test as compared to the non-lithium treated stress-exposed rats. The OFT also showed significant behavioral changes between non-lithium treated stress-exposed rats and the control group (not exposed to stress), i.e., longer immobility time (t=3.618, P=0.022), lower medium speed (t=-3.359, P=0.028), and shorter distance travelled (t=-3.374, P=0.028), but we observed no significant differences between the lithium-treated group and the control group (Fig.1A). In animals exposed to stress and receiving lithium for two weeks, we observed longer active climbing time in FST as compared to non-lithium treated stress-exposed rats, but this difference was not significant (t=2.178, P=0.095, Fig. 1B). We observed significantly reduced active climbing time in non-lithium treated rats exposed to stress compared to the control group (t=-4.230, P=0.013, Fig. 1B). No significant changes were observed between the lithium-treated stress-exposed group and the control group.

Transcriptome changes after two weeks lithium administration

We observed significant gene expression changes in rats exposed to stress and treated with lithium for two weeks compared to the non-lithium treated stress-exposed group (corr P<0.05) in amygdala and blood. We found 13 530 differentially expressed genes in the amygdala (including 360 upregulated and 13 170 downregulated) and 6 473 genes in the blood (including 1 381 upregulated and 5 092 downregulated genes). Among these, the expression of 2806 genes underwent significant changes upon lithium administration in both tissues (P<0.05 and FC>1.5, Fig. 2A). No significant changes in gene expression profile were observed in the hippocampus and frontal cortex. Therefore, in further analysis we compared the expression profiles between amygdala and blood.

To identify the genes significantly altered by chronic lithium administration in brain and in the periphery, we further analyzed 34 genes whose expression was significantly upregulated by lithium in the amygdala and altered in blood. The logistic regression analysis of normalized signal values showed that only the expression of *Alox15* differed significantly in amygdala and blood depending on lithium status (OR=17.028, P=0.016) (Fig. 2B). The other genes were not significantly different between groups in these two tissues. Based on these results, we further investigated *Alox15* expression on mRNA and protein level.

Alox15 mRNA and protein expression

Gene expression analysis by qPCR confirmed that stress-exposed rats receiving lithium had significantly higher expression of *Alox15* in the amygdala than the non-lithium treated stress-exposed group (t=3.972, P=0.016), but no changes were observed between the lithium-treated rats and the control group. We also demonstrated significantly lower expression of *Alox15* (t=-2.823, P=0.047) between non-lithium treated stress-exposed rats and the control group (Fig. 3A).

The gene expression qPCR analysis in blood did not confirm a significant difference between the lithium-treated stress-exposed group and the non-lithium treated stress-exposed group. However, we demonstrated significantly lower expression of *Alox15* (t=-6.648, P=0.003) in the blood of lithium-treated stress-exposed rats compared to the control group (Fig. 3B). Results of the qPCR analysis confirmed the opposite direction of changes in *Alox15* expression between both tissues after lithium treatment, namely increased expression in the amygdala and decreased expression in blood (Fig. 3A, B).

Next, we analyzed the expression of ALOX15 protein in serum and we observed significantly higher expression in the stress-exposed animals receiving lithium (1244.32 ± 101.15 pg/ml) compared to the non-lithium treated stress-exposed group (1008.94 ± 83.23 pg/ml) (t=3.112, P=0.003) (Fig. 3C).

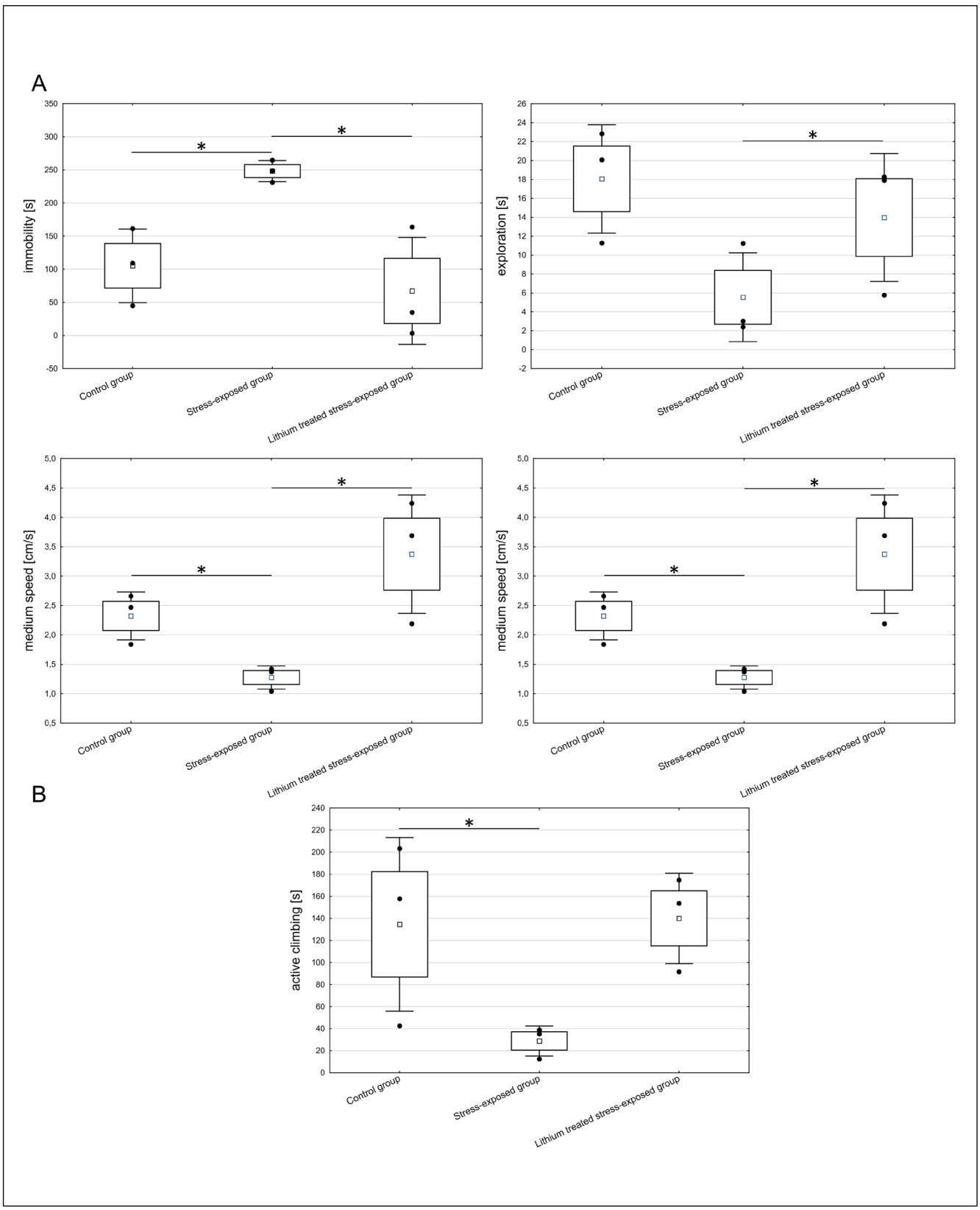

Fig. 1. Behavioral changes in the group of lithium-treated stress-exposed animals compared to non-treated stress-exposed animals, and control group (not exposed to stress); (A) Results of the open field test (OFT); (B) Results of the forced swim test (FST); * indicates significance, boxes indicates mean ± SEM, whiskers indicates mean ± 95% CI, • indicate individual values.

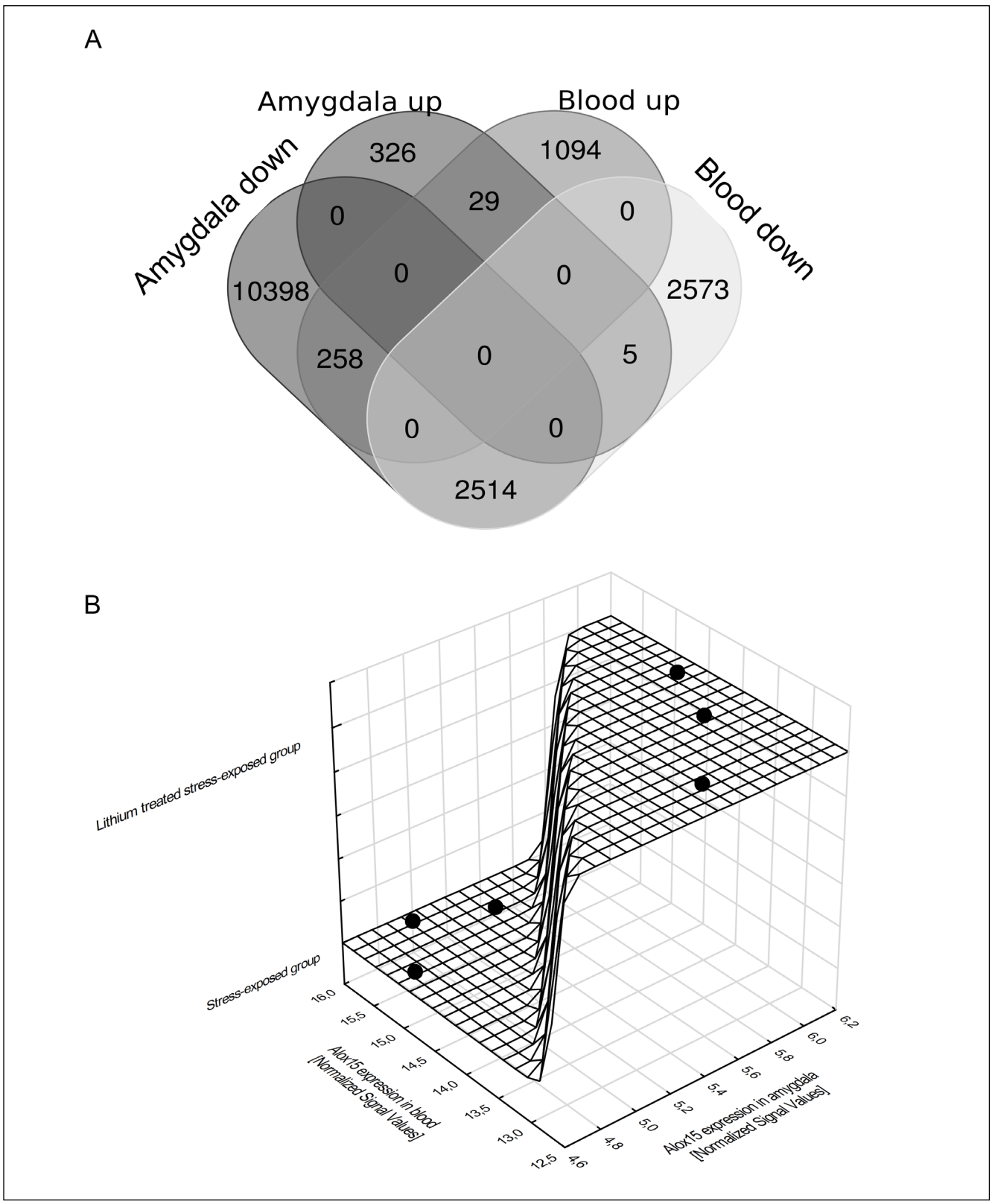

Fig. 2. Transcriptome changes upon lithium treatment of depressive like rats: (A) Differentially expressed genes (up- or downregulated) in stress-exposed rats after two weeks of lithium treatment in amygdala and blood compared to the non-lithium treated stress-exposed group; (B) Expression of the *Alox15* in blood and amygdala of the stress-exposed animal model of depression with and without lithium administration; data on the X and Y axes represent normalized signal values.

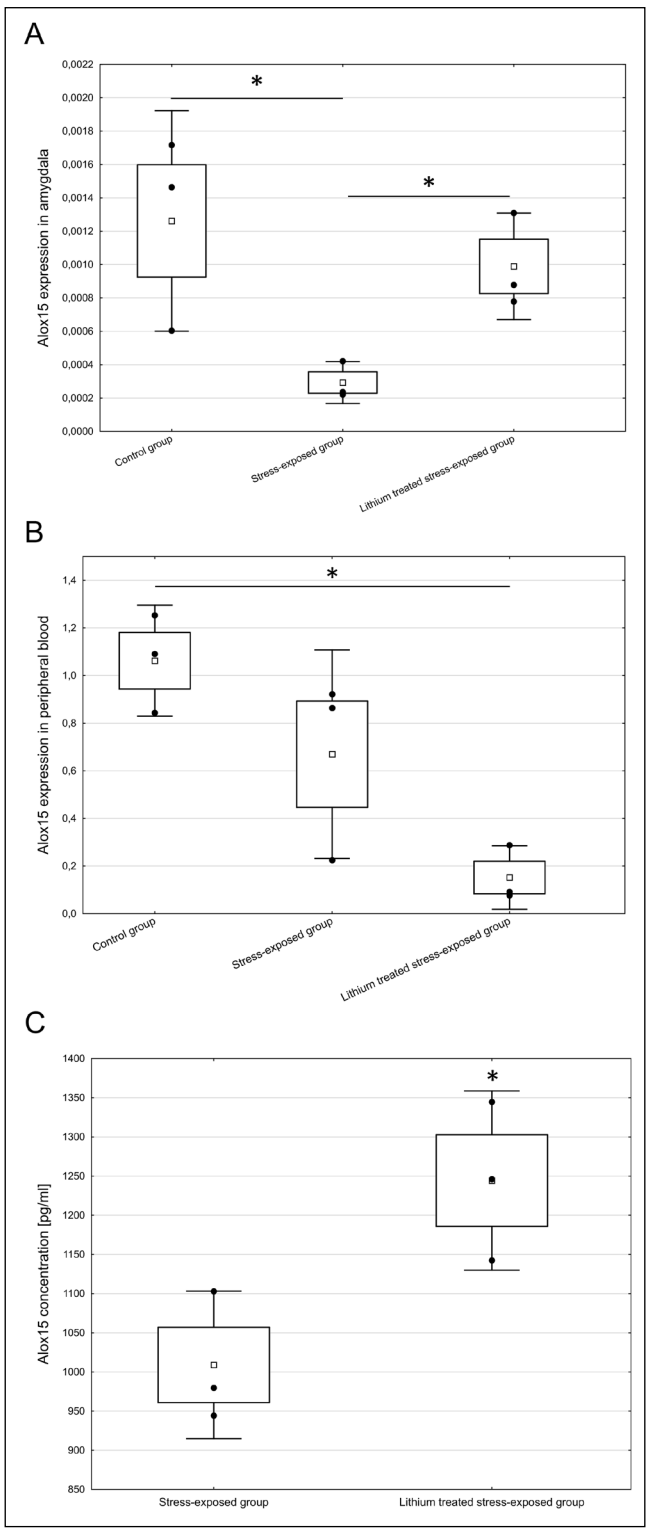

Fig. 3. The expression of *Alox15* mRNA in the amygdala (A) and blood (B) in the group of lithium-treated stress-exposed animals compared to non-treated stress-exposed animals, and control group (not exposed to stress), and change in the serum protein concentration of ALOX15 (C) in the group of lithium receiving stress-exposed animals compared to non-treated stress exposed group; * indicates significance, boxes indicates mean ± SEM, whiskers indicates mean ± 95% CI, • indicate individual values.

DISCUSSION

The main finding of this study is the observation that the gene expression profile is significantly altered in the amygdala and blood after chronic lithium administration in a rat model of depression. We also observed that among 34 genes activated by lithium in the amygdala, the expression of *Alox15* undergoes opposite changes between the amygdala and peripheral blood depending on lithium status and may be a potential link of lithium action between the brain and the periphery.

Comparison of the expression profiles between amygdala and blood after chronic lithium treatment in the rat model of depression showed that *Alox15* expression was significantly influenced by lithium, showing upregulation in the amygdala and downregulation in blood. This is consistent with the results of a recently published *in silico* study showing the opposite gene expression pattern between brain and blood in response to lithium (Najafi et al., 2020). These authors found that genes involved in lithium response were enriched in brain tissue, but were downregulated in the blood and immune cells, whereas those enriched in the blood and immune system presented their lowest expression levels in the brain. Interestingly, our results also indicated increased expression of *Alox15* in the brain (amygdala) and downregulation in blood in lithium-treated stress-exposed rats compared to non-stress-exposed control. Thus, the decreased blood expression of *Alox15* after chronic lithium treatment may indicate an immunomodulatory potential of lithium. Currently, there is a lack of experimental studies comparing the gene expression changes between brain regions and peripheral blood during lithium administration.

The *Alox15* gene encodes 15-lipoxygenase, an enzyme involved in synaptic signaling, inflammatory processes, red blood cell maturation and adipocyte differentiation (Ivanov et al., 2015; Tian et al., 2017; Snodgrass et al., 2020). ALOX15 is one of the critical enzymes involved in biosynthesis of lipid-based mediators of inflammatory processes (Serhan 2014; Ivanov et al., 2015; Kuhn et al., 2016; Tian et al., 2017; Snodgrass et al., 2020). Notably, *Alox15* is not expressed in proinflammatory or naïve macrophages, but is present in the pro-resolving polarized macrophages (M2 macrophages) (Snodgrass et al., 2020). Due to its involvement in the inflammatory resolving processes, *Alox15* might be a potential biomarker of any immunomodulatory mode of action of lithium.

The expression of *Alox15* is regulated by Th2 inflammatory cytokines (i.e. IL-4 and IL-13). After stimulation, ALOX15 facilitates the synthesis of spe-

cialized pro-resolving mediator precursors (SPMs) such as 15-hydroxyeicosatetraenoic acid (15-HETE), 17-hydroxydocosahexaenoic acid (17-HDHA) and resolvin D5 (Serhan 2014; Kuhn et al., 2016; Tian et al., 2017; Snodgrass et al., 2020). The role of ALOX15 in resolving brain inflammatory processes was previously presented by Xu et al. (2017), who found that intracerebral hemorrhage (ICH) significantly increased brain expression of *Alox15* (and *Alox12*). This increase resulted in higher concentrations of products of reactions catalyzed by ALOX15 (e.g., 15(S)-HETE) that participate in the inflammation-resolving processes and neuroprotection.

The anti-inflammatory potential of *Alox15* was also observed in a study analyzing mice with *Alox15* deficiency (*Alox15* knock-out) (Kim et al., 2018). These mice presented increased infiltration of proinflammatory macrophages, that led to enhanced inflammation in the dermis and dermal adipose tissue, and disrupted skin integrity. These symptoms disappeared after the treatment with resolvin D2, a product of a reaction catalyzed by ALOX15 (Kim et al., 2018). Interestingly, Uderhardt et al. (2012) demonstrated that *Alox15* expression during the inflammatory state is site-specific for the resident macrophages of the target tissue, but not for blood monocytes. As the brain-resident macrophages, namely microglia, in the amygdala may be involved in the inflammatory processes in depressive disorders, that may explain the upregulation of *Alox15* in the amygdala but downregulated in peripheral blood upon lithium administration.

Conversely, despite the observed trend of lower expression level of the *Alox15* mRNA in peripheral blood after lithium, we found increased protein levels in the serum of lithium-receiving stress-exposed animals compared to the non-lithium treated stress-exposed group. These results may be explained by enhanced translation of ALOX15 induced by lithium, and therefore less *Alox15* transcripts on mRNA level. These observations may also suggest that ALOX15 passes the blood-brain barrier and exert an effect in the amygdala to recover depressive-like symptoms. Additional studies comparing ALOX15 protein levels in the blood and serum will be helpful in further analysis of the influence of lithium treatment. However, to date there are no reports of a direct signaling pathway connecting the ALOX15 and lithium treatment.

The small number of the animals involved is a potential limitation of our pilot study. Further analyses on larger groups are needed to evaluate and confirm our results. In the future, we plan to study how the lithium treatment regulates the inflammatory mediators influenced by ALOX15.

CONCLUSION

Our study suggests that, in the depression model, chronic lithium treatment affects gene expression profiles in the brain (amygdala) and the periphery (blood). In the context of the inflammatory theory of depression, our results may support the anti-inflammatory potential of lithium. The link between the *Alox15* expression in the brain and blood during lithium treatment suggest it may be a new marker of lithium action. Further functional studies assessing the other inflammatory mediators regulating ALOX15 activity in brain and blood are necessary to confirm that ALOX15 plays a role in lithium action.

ACKNOWLEDGEMENT

We would like to thank the staff of the Department of Medical Genetics (in particular Dr Magdalena Socha and Dr Ewelina Bukowska-Olech) for access to the laboratory equipment for microarrays experiments. We would also like to thank Dr Beata Narożna for invaluable help in bioinformatics analyzes.

This research was funded by National Science Centre, Poland, grant number 2016/21/B/NZ5/00148.

REFERENCES

Abou-Saleh MT, Müller-Oerlinghausen B, Coppen AJ (2017) Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. Int J Bipolar Disord 5: 11.

Atcha Z, Rourke C, Neo AH, Goh CW, Lim JS, Aw CC, Browne ER, Pemberton DJ (2010) Alternative method of oral dosing for rats. J Am Assoc Lab Anim Sci 49: 335–343.

Bellivier F, Marie-Claire C (2018) Molecular signatures of lithium treatment: current knowledge. Pharmacopsychiatry 51: 212–219.

Berrettini WH, Nurnberger JI, Hare TA, Simmons-Alling S, Gershon ES, Post RM (1983) Reduced plasma and CSF gamma-aminobutyric acid in affective illness: effect of lithium carbonate. Biol Psychiatry 18: 185–194.

Brzózka MM, Havemann-Reinecke U, Wichert SP, Falkai P, Rossner MJ (2016) Molecular signatures of psychosocial stress and cognition are modulated by chronic lithium treatment. Schizophr Bull 42: S22–S33.

Chetcuti A, Adams LJ, Mitchell PB, Schofield PR (2008) Microarray gene expression profiling of mouse brain mRNA in a model of lithium treatment. Psychiatr Genet 18: 64–72.

Enache D, Pariante CM, Mondelli V (2019) Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun 81: 24–40.

Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, Alloza C, Shen X, et al. (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22: 343–352.

Ivanov I, Kuhn H, Heydeck D (2015) Structural and functional biology of arachidonic acid 15-lipoxygenase-1 (ALOX15). Gene 573: 1–32.

James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I, Suliankatchi Abdulkader R, et al. (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392: 1789–1858.

Kim SN, Akindehin S, Kwon HJ, Son YH, Saha A, Jung YS, Seong JK, Lim KM, Sung JH, Maddipati KR, Lee YH (2018) Anti-inflammatory role of 15-lipoxygenase contributes to the maintenance of skin integrity in mice. Sci Rep 8: 8856.

Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ (2016) The association between olfaction and depression: a systematic review. Chem Senses 41: 479–486.

Krebs CE, Ori APS, Vreeker A, Wu T, Cantor RM, Boks MPM, Kahn RS, Olde Loohuis LM, Ophoff RA (2020) Whole blood transcriptome analysis in bipolar disorder reveals strong lithium effect. Psychol Med 50: 2575–2586.

Kuhn H, Gehring T, Schroter A, Heydeck D (2016) Cytokine-dependent expression regulation of ALOX15. J Cytokine Biol 1: 1–14.

Leschiner S, Weizman R, Shoukrun R, Veenman L, Gavish M (2000) Tissue-specific regulation of the peripheral benzodiazepine receptor by antidepressants and lithium. Neuropsychobiology 42: 127–134.

Li J, Lu WQ, Beesley S, Loudon ASI, Meng QJ (2012) Lithium impacts on the amplitude and period of the molecular circadian clockwork. PLoS One 7: 33292.

Maletic V, Raison C (2014) Integrated neurobiology of bipolar disorder. Front Psychiatry 5: 98.

Malhi GS, Mann JJ (2018) Depression. Lancet 392: 2299–2312.

McQuillin A, Rizig M, Gurling HMD (2007) A microarray gene expression study of the molecular pharmacology of lithium carbonate on mouse brain mRNA to understand the neurobiology of mood stabilization and treatment of bipolar affective disorder. Pharmacogenet Genomics 17: 605–617.

Najafi H, Totonchi M, Sadeghizadeh M (2020) Predicted cellular and molecular actions of lithium in the treatment of bipolar disorder: an in silico study. CNS Drugs 34: 521–533.

Papp M (2012) Models of affective illness: chronic mild stress in the rat. Curr Protoc Pharmacol 57; 5.9.1–5.9.11.

Penner-Goeke S, Binder EB (2019) Epigenetics and depression. Dialogues Clin Neurosci 21: 397–405.

Perveen T, Haider S, Mumtaz W, Razi F, Tabassum S, Haleem DJ (2013) Attenuation of stress-induced behavioral deficits by lithium administration via serotonin metabolism. Pharmacol Reports 65: 336–342.

Rybakowski JK (2020) Lithium – past, present, future. Int J Psychiatry Clin Pract 24: 330–340.

Sakrajda K, Szczepankiewicz A (2021) Inflammation-related changes in mood disorders and the immunomodulatory role of lithium. Int J Mol Sci 22: 1–15.

Serhan CN (2014) Pro-resolving lipid mediators are leads for resolution physiology. Nature 510: 92–101.

Snodgrass RG, Benatzy Y, Schmid T, Namgaladze D, Mainka M, Schebb NH, Lütjohann D, Brüne B (2020) Efferocytosis potentiates the expression of arachidonate 15-lipoxygenase (ALOX15) in alternatively activated human macrophages through LXR activation. Cell Death Differ 28: 1301–1316.

Szczepankiewicz A, Leszczyńska-Rodziewicz A, Pawlak J, Rajewska-Rager A, Wilkosc M, Zaremba D, Dmitrzak-Weglarz M, Skibinska M, Hauser J (2013) Epistatic interaction between CRHR1 and AVPR1b variants as a predictor of major depressive disorder. Psychiatr Genet 23: 239–246.

Szczepankiewicz D, Celichowski P, Kołodziejski PA, Pruszyńska-Oszmałek E, Sassek M, Zakowicz P, Banach E, Langwiński W, Sakrajda K, Nowakowska J, Socha M, Bukowska-Olech E, et al. (2021a) Transcriptome changes in three brain regions during chronic lithium administration in the rat models of mania and depression. Int J Mol Sci 22: 1148.

Szczepankiewicz D, Narożna B, Celichowski P, Sakrajda K, Kołodziejski P, Banach E, Zakowicz P, Pruszyńska-Oszmałek E, Pawlak J, Wiłkość M, Dmitrzak-Węglarz M, Skibińska M, et al. (2021b) Genes involved in glucocorticoid receptor signalling affect susceptibility to mood disorders. World J Biol Psychiatry 22: 149–160.

Tian R, Zuo X, Jaoude J, Mao F, Colby J, Shureiqi I (2017) ALOX15 as a suppressor of inflammation and cancer: lost in the link. Prostaglandins Other Lipid Mediat 132: 77–83.

Uderhardt S, Herrmann M, Oskolkova O V., Aschermann S, Bicker W, Ipseiz N, Sarter K, Frey B, Rothe T, Voll R, Nimmerjahn F, Bochkov VN, et al. (2012) 12/15-lipoxygenase orchestrates the clearance of apoptotic cells and maintains immunologic tolerance. Immunity 36: 834–846.

Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH, Tan D, Baldessarini RJ (2019) Lithium treatment for unipolar major depressive disorder: systematic review. J Psychopharmacol 33: 167–176.

Xu R, Wang S, Li W, Liu Z, Tang J, Tang X (2017) Activation of peroxisome proliferator-activated receptor-γ by a 12/15-lipoxygenase product of arachidonic acid: A possible neuroprotective effect in the brain after experimental intracerebral hemorrhage. J Neurosurg 127: 522–531.