Univerzita Karlova

1. lékařská fakulta

Autoreferát disertační práce

UNIVERZITA KARLOVA
1. lékařská fakulta

Psychopathology, mental disorders and mitochondrial disorders

Ekaterina Sigitova, M.Sc.

2017

Doktorské studijní programy v biomedicíně

Univerzita Karlova a Akademie věd České republiky

Obor: Psychologie

Předseda oborové rady: Prof. MUDr. Jiří Raboch, DrSc.

Školicí pracoviště: Psychiatrická klinika, 1. lékařská fakulta, Univerzita Karlova v Praze

Školitel: Prof. MUDr. Jiří Raboch, DrSc.

Seznam publikací

1. publikace *in extenso,* které jsou podkladem disertace

a) s impact factorem (uvést hodnotu IF)

1. Sigitova E, Fišar Z, Hroudová J, Cikánková T, Raboch J. Biological hypotheses and biomarkers of bipolar disorder. Psychiatry Clin Neurosci. 2016 Oct 31. doi: 10.1111/pcn.12476. [Epub ahead of print] Review. (IF=2.025)

2. Cikánková T, Sigitova E, Zvěřová M, Fišar Z, Raboch J, Hroudová J. Mitochondrial dysfunctions in bipolar disorder: effect of the disease and pharmacotherapy. CNS Neurol Disord Drug Targets. 2016 Dec 13. [Epub ahead of print] (IF=2.188)

3. Sigitova E. Mitochondrial dysfunction in the pathogenesis of the bipolar disorder. Mental Health, # 12 (127), p. 73-81. (článek v Ruštině) (IF=0.291)

b) bez IF

1. Hroudová J, Fišar Z, Kališová L, Kitzlerová E, Zvěřová M, Sigitová E, Hansíková H, Raboch J. Biologické markery sledované u bipolární afektivní poruchy. Duševní zdraví – věc veřejná. Sborník příspěvků XI. sjezdu Psychiatrické společnosti ČLS JEP s mezinárodní účastí (pořadatelé Anders M, Zrzavecká I, Doubek P). Tribun EU, 2016: 230-232. Poster na XI. sjezdu Psychiatrické společnosti ČLS JEP s mezinárodní účastí

2. Hroudová J, Fišar Z, Kališová L, Kitzlerová E, Zvěřová M, Sigitová E, Hansíková H, Raboch J. Mitochondrial respiration in bipolar affective disorder. ECNP 2016. Poster na 29 th ECNP Congress, 17-20 September 2016, Vienna

3. Raboch J, Hroudová J, Sigitova E, Hansíková H, Fišar Z, Kalisova L, Kitzlerova E, Zvěřová M. Mitochondrial respiration in bipolar affective disorder. IFMAD 2016. Poster na 16 th International Forum on Mood and Anxiety Disorders, Rome, 8-10 December 2016

435. Zhang X., Zhang Z. et al. Effect of treatment on serum glial cell line-derived neurotrophic factor in bipolar patients. J. Affect. Disord. 2010; 126: 326–329.
436. Zhang Z.G., Zhang L. et al. VEGF enhances angiogenesis and promotes blood–brain barrier leakage in the ischemic brain. J. Clin. Invest. 2000; 106: 829–838.
437. Zhu X., Peng X. et al. Pathogenic mutations of nuclear genes associated with mitochondrial disorders. Acta Biochim. Biophys. Sin. 2009. 41, 179–187.
438. Zoratti M., Szabo J. The mitohondrial permeability transition. Biochem. Biophys Acta, 1995, v. 1241, p. 39.

Obsah disertaci

423. Welch K.M., Barkley G.L. et al. Central neurogenic mechanisms of migraine. Neurology 1993; 43 6 Suppl 3: S21−S25.
424. Winsberg M.E., Sachs N. et al. Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. Biol Psychiatry 2000; 47: 475−481.
425. Wong L.J. Pathogenic mitochondrial DNA mutations in protein-coding genes. Muscle Nerve. 2007. 36, 279–293.
426. Wonnapinij P., Chinnery P.F., Samuels D.C. The distribution of mitochondrial DNA heteroplasmy due to random genetic drift. Am. J. Hum. Genet. 2008. 83, 582–593.
427. Yang M.Y., Bowmaker M. et al. Biased incorporation of ribonucleotides on the mitochondrial L-strand accounts for apparent strand-asymmetric DNA replication. Cell 2002; 111: 495–505.
428. Yee C., Yang W., Hekimi S. The intrinsic apoptosis pathway mediates the pro-longevity response to mitochondrial ROS in C.elegans. Cell.2014.157.897-909.
429. Yildiz A., Sachs G.S. et al. ^{31}P nuclear magnetic resonance spectroscopy findings in bipolar illness: a meta-analysis. Psychiatry Res 2001; 106: 181−191.
430. Zarate C.A., Singh J., Manji H.K. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. Biol Psychiatry 2006;59:1006-20.
431. Zeviani M., Ballabio A. et al. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell. 1998;93:973–83.
432. Zeviani M., Bottani E., Viscomi C. Emerging concepts in the therapy of mitochondrial disease. 2015 Mar 10;1847(6-7):544-557.
433. Zeviani M., Carelli V. Mitochondrial disorders. Curr Opin Neurol 2003; 16: 585–94.
434. Zeviani M., Di Donato S. Brain. Mitochondrial disorders. 2004 Oct; 127(Pt 10):2153-72.

412. Wallace D.C. Mitochondrial diseases in man and mouse. Science 1999; 283: 1482–7.
413. Wallace D.C., Greenberg B.D. et al. Sequence analysis of cDNAs for the human and bovine ATP synthase beta subunit: mitochondrial DNA genes sustain seventeen times more mutations. Curr. Genet. 1987. 12, 81–90.
414. Wallace D.C. Mitochondrial genetics: a paradigm for aging and degenerative diseases? Science, 1992. 256, 628–632.
415. Walz J.C., Magalhães P.V. et al. Increased serum neurotrophin-4/5 levels in bipolar disorder. J. Psychiatr. Res. 2009; 43: 721–723.
416. Wang J.F., Shao L. et al. Glutathione S-transferase is a novel target for mood stabilizing drugs in primary cultured neurons. J Neurochem 2004;88:1477-84.
417. Wang Z., Li Z. et al. Association between brainderived neurotrophic factor genetic polymorphism Val66Met and susceptibility to bipolar disorder: A metaanalysis. BMC Psychiatry 2014; 14: 366.
418. Washizuka S., Iwamoto K. et al. Expression of mitochondrial complex I subunit gene NDUFV2 in the lymphoblastoid cells derived from patients with bipolar disorder and schizophrenia. Neurosci Res. 2009;63:199–204.
419. Washizuka S., Kakiuchi C. et al. Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet. 2003b;120B:72–78.
420. Wasserman M.J., Corson T.W. et al. Chronic lithium treatment attenuates intracellular calcium mobilization. Neuropsychopharmacol. 2004;29:759–69.
421. Wei Z., Mousseau D.D. et al. Atypical antipsychotics attenuate neurotoxicity of beta-amyloid (25–35) by modulating Bax and Bcl-X(1/s) expression and localization. J Neurosci Res. 2003;74:942–947.
422. Weinbach E.C., Costa J.L. et al. Effects of tricyclic antidepressant drugs on energy-linked reactions in mitochondria. Biochem Pharmacol 1986;35:1445-51.

Abstrakt v češtině

Projekt je zaměřen poznání souvislosti mitochondrialních patofyziologických procesů s psychopatologickými příznaky při bipolární afektivní poruše (BPD). Změny aktivity vybraných složek dýchacího řetězce a celková respirační rychlost byly měřeny u pacientů s bipolární afektivní poruchou v porovnání s kontrolní skupinou. byly použity diagnostické dotazníky, respirometrie s vysokým rozlišením a metody radiochemické a spektroskopické. Analýzy provedeny u 21 zdravých kontrol a 37 osob s diagnózou bipolární afektivní poruchy (F31). Statistická analýza zahrnovala parametrické a neparametrické analýzy, faktorovou analýzu, jednocestnou analýzu rozptylu a lineární regresní analýzu. Získané výsledky ukázaly velkou roli buněčné energetiky v patofyziologii bipolární poruchy. Mírný rozdíl mezi různými aktivitami mitochondriálních enzymů byl získán u pacientů s manickou a depresivní epizodou onemocnění. Byly také prokázány změny mitochondriálního dýchání u pacientů s BPD ve srovnání se zdravými kontrolami. Mitochondriální respirační indexy u pacientů v remisi ve srovnání se zdravými kontrolními osobami byly změneny v souvislosti s předchozí fází onemocnění. Byla zjištěna souvislost mezi stavem onemocnění, psychopatologickými příznaky, klinickým zlepšením a mitochondriální patologií. Byla stanovena doba trvání mezi akutním manickým stavem a remisí a její závislost na indikátorech mitochondriální patologie.

This study investigates the connection between different pathophysiological processes in mitochondria and psychopathological symptoms in patients with bipolar disorder. Changes in activity of selected components of the respiratory chain and overall respiratory rate of mitochondria were analyzed in patients with bipolar disorder when compared to healthy controls. Diagnostic scales and questionnaires, high-resolution respirometry, radiochemical and spectroscopic methods were used. 37 patients with a diagnosis of bipolar disorder (F31) and 21 healthy volunteers were involved in the study. Statistical analysis included the methods of parametric and nonparametric analysis, factor analysis, one-way analysis of variance and linear regression analysis. Obtained results revealed that cellular energetics plays a great role in the pathophysiology of bipolar disorder. There was a mild difference between different mitochondrial enzymes activity in patients within manic phases and depressive phases of the disease. Changes in mitochondrial respiration in patients with BD as compared to healthy controls were also shown. Mitochondrial respiration indexes for patients with BD in remission as compared to healthy controls were altered in accordance with the previous phase of the disease. Association between the state of the disease, psychopathological symptoms, clinical improvement and mitochondrial pathology was established. The duration period between the acute manic state and remission and its dependence on the mitochondrial pathology indicators was established.

402. Urenjak J., Williams S.R. et al. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J Neurosci 1993; 13: 981−989.
403. Valla J., Schneider I. et al. Impaired platelet mitochondrial activity in Alzheimer's disease and mild cognitive impairment. Mitochondrion 2006. 6:323-30.
404. Valnot I., Kassis J. et al. A mitochondrial cytochrome b mutation but no mutations of nuclearly encoded subunits in ubiquinol cytochrome c reductase (complex III) deficiency. Hum. Genet. 1999. 104, 460–466.
405. Valvassori S.S., Rezin G.T. et al. Effects of mood stabilizers on mitochondrial respiratory chain activity in brain of rats treated with d-amphetamine. J Psychiatr Res. 2010 Oct;44(14):903-9.
406. van Goethem G., Dermaut B. et al. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. Nat Genet. 2001 Jul;28(3):211-2.
407. van Goethem G., Martin J.J., van Broeckhoven C. Progressive external ophthalmoplegia characterized by multiple deletions of mitochondrial DNA: unraveling the pathogenesis of human mitochondrial DNA instability and the initiation of a genetic classification. Neuromolecular Med. 2003. 3, 129–146.
408. Vargas C., López-Jaramillo C., Vieta E. A systematic literature review of resting state network—functional MRI in bipolar disorder. J. Affect. Disord. 2013; 150: 727–735.
409. Vawter M.P., Tomita H. et al. Mitochondrial-related gene expression changes are sensitive to agonal-pH state: implications for brain disorders. Mol Psychiatry. 2006;11:615, 663–679.
410. Vercesi A.E., Castilho R.F. et al. Mitochondrial energy metabolism and redox state in dyslipidemias. Life, April – May 2007. 59(4 – 5): 263 – 268.
411. Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta Psychiatr Scand. 2000 Jan; 101(1):11-20.

391. Thompson R.M., Weickert C.S. et al. Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. J. Psychiatry Neurosci. 2011; 36: 195–203.
392. Thorburn D.R. Mitochondrial disorders: prevalence, myths and advances. J. Inherit. Metab.Dis. 2004. 27. 349-362.
393. Thorburn D.R., Dahl H.H. Mitochondrial disorders: genetics, counseling, prenatal diagnosis and reproductive options. Am J Med Genet 2001; 106: 102–14.
394. Tramontina J.F., Andreazza A.C. et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci. Lett. 2009; 452: 111–113.
395. Truckenmiller M.E., Namboodiri M.A. et al. N-acetylation of L-aspartate in the nervous system: differential distribution of a specific enzyme. J Neurochem 1985; 45: 1658−1662.
396. Turecki G., Grof P. et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry 2001. 6: 570–578.
397. Turnbull H.E., Lax N.Z. et al. The mitochondrial brain: From mitochondrial genome to neurodegeneration. Bio/chim. Biophys. Acta. 2010. 1802, 111–121.
398. Turrens J.F. Mitochondrial formation of reactive oxygen species. J. Physiol. 2003. 552, 335 – 344.
399. Uehara N., Mori M. et al. New MT-ND6 and NDUFA1 mutations in mitochondrial respiratory chain disorders. Ann Clin Transl Neurol. May 2014; 1(5): 361–369.
400. Uher R. Gene–environment interactions in severe mental illness. Front. Psychiatry 2014; 5: 48.
401. Ukai W., Ozawa H. et al. Neurotoxic potential of haloperidol in comparison with risperidone: implication of Akt-mediated signal changes by haloperidol. J Neural Transm. 2004;111:667–681.

1. Úvod

Mental disorders are a big group of complex and serious diseases affecting mainly the psychic sphere and are characterized by a high prevalence, difficulties with the diagnosis, high levels of disability and mortality, a significant societal cost and different serious risks for the patients.

During the last decades many publications revealed an increasing need for further research on this topic because of characteristics such as frequent life-threatening conditions, urgent intervention requirement, clinical pathomorphosis, prolonged duration and a delayed treatment response postulate a problem of mental disorders as one of the central problems of modern psychiatry and general medical practice. Psychopathological symptoms also often cause a significant impairment of social functioning which may have an irreversible affect on patient's life.

Although research is ongoing many important questions still remain open. Questions of early diagnosis and prevention, clinical assessment of the symptoms, therapeutic approaches and pathomorphological mechanisms undermining the disease continue to be unanswered. One of these questions is a comprehensive study of typical pathogenetic features

associated with the psychopathological symptoms of the disease, including cell mechanisms.

Cell respiration in psychiatric disorders had been a subject of large research interest for many years as the nerve tissue is highly dependent on oxidative metabolism because of a high energy demand and thus the brain is extremely vulnerable to an insufficient ATP production. Many researchers found evidence for mitochondrial dysfunction and oxidative stress in different mental disorders, although most of the patients do not have any 'classical' mitochondrial disease.

Mood disorders are one of the main focuses in mitochondria-related research since 2000 when Dr. Kato offered a mitochondrial hypothesis based on the findings that patients with bipolar disorder have an abnormal energy metabolism and abnormal mitochondrial DNA in the brain.

Mood disorders (depressive, manic and bipolar disorders) are very common illnesses, often with recurrent or chronic courses. Their pathophysiology is not yet well known. There is currently no reliable biochemical, genetic, physiological or other biological test to diagnose bipolar affective disorder or to predict the success of pharmacotherapy.

The etiology of mood disorders, including BPD, remains uncertain. Both genetic background and environmental factors, such as stressful life events or substance abuse, are

spectroscopy research. Molecular Psychiatry. 2005. 10, 900–919.
380. Strakowski S.M., DelBello M.P et al. Neuroimaging in bipolar disorder. Bipolar Disord. 2000 Sep; 2(3 Pt 1):148-64.
381. Strakowski S.M., DelBello M.P. et al. Ventricular and periventricular structural volumes in firstversus multiple-episode bipolar disorder. Am. J. Psychiatry 2002; 159: 1841–1847.
382. Sue C.M., Quigley A. Detection of MELAS A3243G point mutation in muscle, blood and hair follicles. J. Neurol. Sci. 1998. 161, 36–39.
383. Sukhorukov V.S. The mitochondrial pathology and problems of pathophysiology of mental disorders. Zh Nevrol Psikhiatr Im S S Korsakova. 2008;108(6):83-90.
384. Sun X., Wang J.F. et al. Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. J Psychiatry Neurosci. 2006 May; 31(3):189-96.
385. Suomalainen A. et al. An autosomal locus predisposing to deletions of mitochondrial DNA. Nat Genet. 1995 Feb;9(2):146-51.
386. Susin S.A., Lorenzo N.K. et al. Molecular characterization of mitochondrial apoptosis-inducing factor. Nature, 1999, v. 397, p. 441-446.
387. Suzuki T., Koizumi J. et al. Mitochondrial encephalomyopathy (MELAS) with mental disorder. CT, MRI and SPECT findings. Neuroradiology 1990; 32:1: 74—76.
388. Taanman J.W. The mitochondrial genome: structure, transcription, translation and replication. Biochim. Biophys. Acta 1999. 1410, 103–123.
389. Tein I. Disorders of fatty acid oxidation. In: Handbook of Clinical Neurology, 2013. 113: 1675–1688.
390. Thomeer E.C., Verhoeven W.M. et al. Psychiatric symptoms in MELAS; a case report. J Neurol Neurosurg Psychiat 1998; 64: 692—693.

368. Sickmann A., Reinders J. et al. The proteome of Saccharomyces cerevisiae mitochondria. Proc. Natl. Acad. Sci.USA 2000. 100, 13207–13212.
369. Silva M.F., Aires C.C. et al. Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: a review. J Inherit Metab Dis. 2008 Apr; 31(2):205-16.
370. Silverstone P.H., Wu R.H. et al. Chronic treatment with both lithium and sodium valproate may normalize phosphoinositol cycle activity in bipolar patients. Hum Psychopharmacol 2002; 17: 321−327.
371. Silvestri G., Ciafaloni E. et al. Clinical features associated with the A-->G transition at nucleotide 8344 of mtDNA ("MERRF mutation"). Neurology. 1993 (43), 1200–1206.
372. Skaper S.D. The biology of neurotrophins, signalling pathways, and functional peptide mimetics of neurotrophins and their receptors. CNS Neurol. Disord. Drug Targets 2008; 7: 46–62.
373. Skulachev V.P. Mitochondria in the programmed death phenomena; a principle of biology: "It is better to die than to be wrong". IUBMB Life, 2000. v. 49. p. 365-373.
374. Soeiro-de-Souza M.G., Andreazza A.C. et al. Soeiro-de-Souza M.G., Andreazza A.C. et al. Number of manic episodes is associated with elevated DNA oxidation in bipolar I disorder. Int J Neuropsychopharmacol. 2013 Aug; 16(7):1505-12.
376. Squassina A., Costa M. et al. Insulin-like growth factor 1 (IGF-1) expression is up-regulated in lymphoblastoid cell lines of lithium responsive bipolar disorder patients. Pharmacol. Res. 2013; 73: 1–7.
377. Stahl A. A current review of fatty acid transport proteins (SLC27). Pflugers Arch. 2004. 447 (5): 722–7.
378. Stine O.C., Luu S.U., Zito M. The possible association between affective disorder and partially deleted mitochondrial DNA. Biol Psychiat 1993; 33: 141—142.
379. Stork C., Renshaw P.F. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance

related to the risk of development of BPD (Uher R, 2014). Insights into the processes underlying neuroprogression in BPD have been provided by studies examining genetic and epigenetic changes, structural and functional changes in the brain, damage in neuronal circuits, disturbed circadian rhythms, changes in immune and endocrine systems, impairment in neuronal plasticity and resilience, increased apoptosis, disturbances of synaptic transmission and signal transduction, activation of neurotoxic mechanisms, and changes in neurogenesis (Berk M et al, 2014). Pathways underlying neuroprogression in BPD include the dopaminergic system, inflammatory cytokines, oxidative and nitrosative stress, mitochondrial dysfunction and endoplasmic reticulum stress, alterations in cAMP response element-binding protein (CREB) and neurotrophic system, dysregulation of calcium signaling, neuroin- flammation, autoimmune processes, tryptophan and tryptophan metabolites, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation. (Berk M et al, 2011; Anderson G, Maes M, 2015; Andreazza AC, Young LT, 2014)

Research for biological markers of bipolar affective disorder is based on a current mood hypothesis that the activity of monoaminergic neurotransmitter systems, energy cell metabolism, growth factor and other components affecting neuronal plasticity. Nerve cells need an extraordinarily large

amount of cellular energy to provide for the synthesis of molecules that allow them to receive, process and transmit information, develop axonal and dendritic branches, and create new synaptic connections. Therefore, the hypothesis of mitochondrial dysfunction is a prospective hypothesis for a number of diseases including bipolar affective disorder.

The aim of the following research is to determine the connection between selected mitochondrial functions and psychopathological symptoms during the disease, i.e. in manic, depressive and remission episodes of the bipolar disorder.

357. Shao L., Martin M.V. et al. Mitochondrial involvement in psychiatric disorders. Ann Med. 2008; 40(4): 281–295.
358. Shao L., Young L.T., Wang J.F. Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells. Biol Psychiatry. 2005;58:879–84.
359. Shapira Y., Harel S., Russell A. Mitochondrial encephalomyopathies: a group of neuromuscular disorders with defects in oxidative metabolism. Isr J Med Sci. 1977 Feb;13(2):161-4.
360. Sharma R., Venkatasubramanian P.N. et al. Proton magnetic resonance spectroscopy of the brain in schizophrenic and affective patients. Schizophr Res 1992; 8: 43−49.
361. Shibata T., Yamagata H. et al. The alteration of hypoxia inducible factor-1 (HIF-1) and its target genes in mood disorder patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 2013; 43: 222–229.
362. Shoffner J.M., Lott M.T. et al. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. Cell. 1990. 6, 931–937.
363. Shoffner J.M., Wallace D.C. Oxidative phosphorylation diseases. In: The metabolic and molecular bases of inherited disease. 7th edition, McGraw-Hill, New York 1995; 1535—1629.
364. Shoubridge E.A., Wai T. Mitochondrial DNA and the mammalian oocyte. Curr. Top. Dev. Biol. 2007. 77, 87–111.
365. Shuster R.C., Rubenstein A.J., Wallace D.C. Mitochondrial DNA in anucleate human blood cells. Biochem Biophys Res Commun. 1988 Sep 30;155(3):1360-5.
366. Shy G.M., Gonatas N.K. Human myopathy with giant abnormal mitochondria. Science. 1964. Jul 31;145:493-6.
367. Siciliano G., Tessa A. et al. Autosomal dominant external ophthalmoplegia and bipolar affective disorder associated with a mutation in theANT1 gene. Neuromuscul Disord. 2003;13:162–165.

346. Schmidt O., Pfanner N., Meisinger, C. Mitochondrial protein import: from proteomics to functional mechanisms. Nat. Rev. Mol. Cell Biol. 2010. 11, 655–667.
347. Schmitt K., Holsboer-Trachsler E., Eckert A. BDNF in sleep, insomnia, and sleep deprivation. Ann. Med. 2016; 48: 42–51.
348. Schon E.A., Bonilla E., DiMauro S. Mitochondrial DNA mutations and pathogenesis. J Bioenerg Biomembr. 1997 Apr;29(2):131-49.
349. Schwartz M., Vissing, J. New patterns of inheritance in mitochondrial disease. Biochem. Biophys. Res. Commun. 2003. 310, 247–251.
350. Scola G., Andreazza A.C. Current state of biomarkers in bipolar disorder. Curr. Psychiatry Rep. 2014; 16: 514.
351. Scola G., Andreazza A.C. The role of neurotrophins in bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 2015; 56: 122–128.
352. Scola G., Kim H.K. et al. A fresh look at complex I in microarray data: clues to understanding disease-specific mitochondrial alterations in bipolar disorder. Biol Psychiatry. 2012 S0006-3223(12)00583-5.
353. Selvaraj S., Murthy N.V. et al. Diminished brain 5-HT transporter binding in major depression: A positron emission tomography study with [11C]DASB. Psychopharmacology (Berl) 2011; 213: 555–562.
354. Sen S., Duman R., Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. Biol. Psychiatry 2008; 64: 527–532.
355. Serretti A., Mandelli L. The genetics of bipolar disorder: Genome 'hot regions,' genes, new potential candidates and future directions. Mol. Psychiatry 2008; 13: 742–771.
356. Shalbuyeva N., Brustovetsky T., Brustovetsky N. Lithium desensitizes brain mitochondria to calcium, antagonizes permeability transition, and diminishes cytochrome C release. Journal of Biological Chemistry. 2007;282:18057–18068.

2. Hypotézy a cíle práce

The review was focused on the data revealing multiple connections between different signs and symptoms of mental disorders and various mitochondrial pathology. We can now see that the interpretation of all these data requires careful attention because it is partially controversial and some effects were observed in certain brain regions which can possibly indicate a result of other influences and not necessarily indicate a direct cause-and-effect relationship. Obviously the role of mitochondria in the pathogenesis of mental disorders is very complicated and might be different in different brain regions with maximum observed effects in the most vulnerable domains for each disease.

Some promising results were obtained leading to perspective studies addressing deeper connections between mitochondrial functions and the pathology of mood disorders. A complex view of the pathology of mood disorders and the role of mitochondria in them is crucially important to develop new diagnostic tools and various therapeutic strategies for this group of devastating diseases. Mitochondrial parameters can be also evaluated as biological markers of bipolar disorder, one of the mood disorders.

Summarizing various connections between pathophysiological processes in bipolar disorder and mitochondrial dysfunctions, we state a purpose for the study: to explore how energy metabolism in mitochondria corresponds to clinical evaluation of psychopathological symptoms in patients with bipolar disorder.

Hypotheses of the study:

Hypothesis 1. There is a set of mitochondrial functional impairment indexes specific for the current phase of the disorder.

Hypothesis 2. The severity of the symptoms of bipolar disorder is associated with the severity of the alteration of the mitochondrial function.

Hypothesis 3. There is a difference in the levels of mitochondrial respiration and enzyme activity in manic state and depressive state.

Hypothesis 4. There is a difference in the levels of mitochondrial respiration and enzyme activity in patients with BPD and healthy controls in both the acute state and remission.

335. Sanacora G., Zarate C.A. et al. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discov. 2008; 7: 426–437.
336. Santarelli L., Saxe M. et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003; 301: 805–809.
337. Sapolsky R.M. Is impaired neurogenesis relevant to the affective symptoms of depression? Biol. Psychiatry 2004; 56: 137–139.
338. Sarandol A., Sarandol E. et al. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative system. Hum Psychopharmacol 2007;22:67-73.
339. Saraste M. Oxidative phosphorylation at the fin de siecle. Science 1999; 283: 1488–93.
340. Sauter A., Rudkin T.M. Determination of creatine kinase kinetic parameters in rat brain by NMR magnetization transfer. Correlation with brain function. J Biol Chem 1993; 268: 13166−13171.
341. Savitz J., Drevets W.C. Bipolar and major depressive disorder: Neuroimaging the developmentaldegenerative divide. Neurosci. Biobehav. Rev. 2009; 33: 699–771.
342. Scaini G., Rezin G.T. et al. Mitochondrial dysfunction in bipolar disorder: Evidence, pathophysiology and translational implications. Neurosci and Biobehav Rev. 2016. Vol 68: 694-713.
343. Scarpulla R.C. Nuclear control of respiratory gene expression in mammalian cells. J Cell Biochem. 2006.97(4): 673-83.
344. Schildkraut J.J. The catecholamine hypothesis of affective disorders: A review of supporting evidence. Am. J. Psychiatry 1965; 122: 509–522.
345. Schmidt O., Pfanner N., Meisinger C. Mitochondrial protein import: from proteomics to functional mechanisms. Nat Rev Mol Cell Biol. 2010 Sep; 11(9):655-67.

324. Rodrigues T., Santos A.C. et al. Thioridazine interacts with the membrane of mitochondria acquiring antioxidant activity toward apoptosis--potentially implicated mechanisms. Br J Pharmacol. 2002 May; 136(1):136-42.
325. Rothman D.L. ^{1}H NMR studies of human brain metabolism and physiology. In: Gillies RJ (ed).NMR in Physiology and Biomedicine Academic Press: San Diego, CA 1994; pp 353−372.
326. Rotig A. Genetic bases of mitochondrial respiratory chain disorders. Diabetes Metab. 2010. 36, 97–107.
327. Rötig A., Cormier V. et al. Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. J. Clin. Invest. 1990 (86), 1601–1608.
328. Rötig A., Rustin P. et al. Aconitase and mitochondrial iron-sulphur protein deficiency in Friedreich ataxia. Nat Genet. 1997;17:215–7.
329. Rudkin T.M., Arnold D.L. Proton magnetic resonance spectroscopy for the diagnosis and management of cerebral disorders. Arch Neurol 1999; 56: 919−926.
330. Ryan M.M., Lockstone H.E. et al. Gene expression analysis of bipolar disorder reveals downregulation of the ubiquitin cycle and alterations in synaptic genes. Mol Psychiatry. 2006 Oct;11(10):965-78.
331. Rybakowski J.K., Permoda-Osip A. et al. Single ketamine infusion in bipolar depression resistant to antidepressants: Are neurotrophins involved? Hum. Psychopharmacol. 2013; 28: 87–90.
332. Rybakowski J.K. Response to lithium in bipolar disorder: Clinical and genetic findings. ACS Chem. Nerosci. 2014; 5: 413–421.
333. Sagara Y. Induction of reactive oxygen species in neurons by haloperidol. J Neurochem. 1998 Sep; 71(3):1002-12.
334. Saldoña M., Bonastre M. et al. Differential nigral expression of Bcl-2 protein family in chronically haloperidol and clozapine-treated rats: role in neurotoxicity and stereotyped behavior. Exp Neurol. 2007;203:302–308.

3. Materiál a metodika

3.1. Study design and participants

37 patients with diagnosis of bipolar disorder (F31) according to ICD-10 were recruited from acute wards of the Department of Psychiatry of the First Faculty of Medicine, Charles University and General University Hospital in Prague and repeatedly tested using different psychopathology scales and blood platelets analysis methods (measurement 1 – acute phase, measurement 2 – remission). The control group consisted of 21 healthy volunteers matched by age and gender tested once using blood platelets analysis methods. Demographic data was collected for each person.

The included criteria were as follows:

- all in-patients and out-patients are already treated for BPD (at least second current episode);
- acute state;
- within one week upon hospitalization;
- diagnosis of the BPD – F31 (phase manic, depressive, remission);
- age 18-65.

The excluded criteria were as follows:

- additional diagnosis of any listed in F10-F19, F20-F29, F70-F79;
- psychoactive substance abuse;
- organic brain damage;
- significant cognitive impairment;
- history of medication abuse of any kind;
- diagnosis of cancer or any neoplastic disease within the last 3 years;
- a diagnosed mitochondrial disorder;
- constantly taking medicines such as coenzyme Q, L-carnitine, vitamin E, chloramphenicol, doxycycline, ofloxacin, ciprofloxacin, perofloxacin, azathioprine, cyclosporine, tacrolimus, everolimus, monoclonal antibodies, amiodarone, statins, levomepromazine, haloperidol;
- participation in any study involving investigational drug within the last 3 months.

The study was carried out according to the principles expressed in the Declaration of Helsinki and the study protocol was approved by the Ethical Review Board of the First Faculty of Medicine and General University Hospital in Prague, Czech Republic. Written informed consent was obtained from all participants.

314. Quiroz J.A., Gray N.A. Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology. 2008 Oct; 33(11):2551-65.
315. Rao J.S., Kellom M. et al. Dysregulated glutamate and dopamine transporters in postmortem frontal cortex from bipolar and schizophrenic patients. J. Affect. Disord. 2012; 136: 63–71.
316. Ray M.T., Shannon W.C., Webster M.J. Decreased BDNF and TrkB mRNA expression in multiple cortical areas of patients with schizophrenia and mood disorders. Transl. Psychiatry 2014; 4: 389.
317. Regenold W.T., Phatak P. et al. Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis. Biol Psychiatry. 2009;65:489–494.
318. Reinders J., Zahedi R. et al. Toward the complete yeast mitochondrial proteome: multidimensional separation techniques for mitochondrial proteomics. J. Proteome Res., 5 (2006), pp. 1543–1554.
319. Rezin G.T., Amboni G. et al. Mitochondrial dysfunction and psychiatric disorders. Neurochem Res. 2009 Jun;34(6):1021-9.
320. Rezin G.T., Furlanetto C.B. et al. Fenproporex increases locomotor activity and alters energy metabolism, and mood stabilizers reverse these changes: a proposal for a new animal model of mania. Mol Neurobiol. 2014 Apr;49(2):877-92.
321. Richter C. Oxidative stress, mitochondria, and apoptosis. Restor Neurol Neurosci. 1998 Jun;12(2-3):59-62.
322. Rimoldi M., Zeviani M. et al. Loss of ETHE1, a mitochondrial dioxygenase, causes fatal sulfide toxicity in ethylmalonic encephalopathy. Nat Med. 2009;15:200–5.
323. Rivera M., Gutiérrez B. et al. High-activity variants of the uMAOA polymorphism increase the risk for depression in a large primary care sample. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2009; 150: 395–402.

304. Plátenník J., Fišar Z. et al. GSK3β, CREB, and BDNF in peripheral blood of patients with Alzheimer's disease and depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014; 50: 83–93.
305. Polyakova M., Stuke K. et al. BDNF as a biomarker for successful treatment of mood disorders: A systematic and quantitative meta-analysis. J. Affect. Disord. 2015; 174: 432–440.
306. Poovathingal S.K., Gruber J. et al. Stochastic drift in mitochondrial DNA point mutations: a novel perspective ex silico. Plos Computational Biology. 2009;5(11). Epub.
307. Poulton J., Turnbull D.M. 74th ENMC international workshop: mitochondrial diseases 19-20 November 1999, Naarden, the Netherlands. Neuromuscul Disord 1. 2000. 10: 460-462.
308. Poyton, R.O., McEwen, J.E. Cross-talk between nuclear and mitochondrial genomes. Ann. Rev. Biochem. 1996. 65: 563-607.
309. Prince J.A., Harro J. et al. Putamen mitochondrial energy metabolism is highly correlated to emotional and intellectual impairment in schizophrenics. Neuropsychopharmacol. 2000 Mar; 22(3):284-92.
310. Prince J.A., Yassin M.S., Oreland L. A histochemical demonstration of altered cytochrome oxidase activity in the rat brain by neuroleptics. Eur Neuropsychopharmacol 1998;8:1-6.
311. Prince J.A., Yassin M.S., Oreland L. Neuroleptic-induced mitochondrial enzyme alterations in the rat brain. J Pharmacol Exp Ther. 1997a;280:261–267.
312. Prince J.A., Yassin M.S., Oreland L. Normalization of cytochrome-c oxidase activity in the rat brain by neuroleptics after chronic treatment with PCP or methamphetamine. Neuropharmacology 1997;36:1665-78.
313. Quiroz J.A., Gray N.A. et al. Novel Insights into Lithium's Mechanism of Action: Neurotrophic and Neuroprotective Effects. Neuropsychobiology. 2010 Jun; 62(1): 50–60.

3.2. Questionnaires and scales

All patients included were screened for bipolar disorder using the mood disorder questionnaire (MDQ) (Hirschfeld RM et al, 2000).

The Mood Disorder Questionnaire is a brief, self-report screening instrument for bipolar disorder with both good sensitivity and very good specificity which includes 13 questions plus items assessing clustering of symptoms and functional impairment.

Severity of current depression was tested using the MADRS (Montgomery–Åsberg Depression Rating Scale).

MADRS is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders. It was designed in 1979 by British and Swedish researchers as an adjunct to the Hamilton Rating Scale for Depression to be more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale.

A higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60. The questionnaire includes questions on the following symptoms 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite

6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts.

Severity of current mania was tested using the Young Scale of Mania (YMRS).

YMRS is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. The scale is generally done by a clinician or trained rater with expertise of manic patients and takes 15–30 minutes to complete.

Severity of illness

General severity of illness was assessed using Clinical Global Impression - Improvement scale (CGI-I). CGI-I is a 7-point scale that requires the clinician to rate the improvement of the patient's mental illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

disorder patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 2013; 44: 29–33.
294. Pan W., Banks W.A. et al. Transport of brain-derived neurotrophic factor across the blood–brain barrier. Neuropharmacology 1998; 37: 1553–1561.
295. Pan W., Banks W.A., Kastin A.J. Permeability of the blood– brain barrier to neurotrophins. Brain Res. 1998b; 788: 87–94.
296. Pan W., Kastin A.J. et al. Saturable entry of ciliary neurotrophic factor into brain. Neurosci. Lett. 1999; 263: 69–71.
297. Pan W., Kastin A.J. Interactions of IGF-1 with the blood–brain barrier in vivo and in situ. Neuroendocrinology 2000; 72: 171–178.
298. Patel T.B., Clark J.B. Synthesis of N-acetyl-L-aspartate by rat brain mitochondria and its involvement in mitochondrial/cytosolic carbon transport. Biochem J 1979; 184: 539−546.
299. Pereira A.C., McQuillin A. et al. Genetic association and sequencing of the insulin-like growth factor 1 gene in bipolar affective disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2011; 156: 177–187.
300. Pérez V.I., Bokov A. et al. Is the oxidative stress theory of aging dead? Biochimica Et Biophysica Acta. 2009;1790(10) 1005-14.
301. Perry D.C., Sturm V.E. et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. J. Neurosurg. 2016; 124: 511–526.
302. Picard M., Shirihai O.S. et al. Mitochondrial morphology transitions and functions: implications for retrograde signaling? Am J Physiol Regul Integr Comp Physiol. 2013 Mar 15; 304(6): R393–R406.
303. Pittenger C., Duman R.S. Stress, depression, and neuroplasticity: A convergence of mechanisms. Neuropsychopharmacology 2008; 33: 88–109.

282. Neupert W., Herrmann J.M. Translocation of proteins into mitochondria. Annu. Rev. Biochem. 2007. 76, 723–749.
283. Nonaka S., Hough C.J., Chuang D.M. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. Proc Natl Acad Sci U S A. 1998;95:2642–7.
284. Norby S., Lestienne P. et al. Juvenile Kearns-Sayre syndrome initially misdiagnosed as a psychosomatic disorder. J Med Genet 1994; 31: 45—50.
285. Nouws J., Wibrand F. et al. A patient with complex I deficiency caused by a novel ACAD9 mutation not responding to riboflavin treatment. JIMD Rep., 12 (2014), pp. 37–45.
286. Nunnari J., Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148(6):1145-59.
287. Ohara K., Isoda H. et al.. Proton magnetic resonance spectroscopy of the lenticular nuclei in bipolar I affective disorder. Psychiatry Res 1998; 84: 55−60.
288. Olson W., Engel W.K. et al. Oculocraniosomatic neuromuscular disease with ‘ragged-red’ fibers. Arch Neurol. 1972 Mar 26 (3): 193-211.
289. Onishi H., Kawanishi C. et al. Depressive disorder due to mitochondrial transfer RNALeu(UUR) mutation. Biol Psychiat 1997; 41: 1137—1139.
290. Orrenius S., Gogvadze V., Zhivotovsky, B. Mitochondrial oxidative stress: implications for cell death. Annu. Rev. Pharmacol. Toxicol. 2006. 47, 143 – 183.
291. Ozaki N., Chuang D.M. Lithium increases transcription factor binding to AP-1 and cyclic AMP-responsive element in cultured neurons and rat brain. J Neurochem. 1997;69:2336–44.
292. Pagliarini D.J., Calvo S.E. et al. A mitochondrial protein compendium elucidates complex I disease biology. Cell, 134 (2008), pp. 112–123.
293. Palomino A., González-Pinto A. et al. Relationship between negative symptoms and plasma levels of insulin-like growth factor 1 in first-episode schizophrenia and bipolar

Psychopathology symptoms were evaluated twice during the illness (before treatment, in acute state, and during treatment, in remission).

3.3. Laboratory methods

Peripheral blood samples were taken from the antecubital vein of each participant between 7:00 and 8:00 am, when all subjects were nicotine- and and coffee-free, before their morning medications. 24 milliliters of blood were drawn into BD Vacutainer® blood collection tubes with anticoagulant. Platelet rich plasma was separated by centrifugation at 200×g for 10 min at 25 °C. Platelets were counted by microscopy using a counting chamber and immediately used for measuring of mitochondrial parameters.

The energy metabolism related to mitochondrial dysfunctions was analyzed in biochemical laboratories (First Faculty of Medicine). Selected mitochondrial parameters (citrate synthase and electron transport chain complexes activities, ATP production and mitochondrial respiratory rate) and functional changes in monoaminergic system (MAO activity, serotonin uptake) were measured in peripheral blood components. High-resolution respirometry, fluorescence, radiochemical and spectrophotometric methods were used.

Complexes of ETS – complex I, II, II+III and IV and citrate synthase were measured spectrophotometrically (Hroudová and Fišar, 2010). The relative activities of mitochondrial complexes were expressed as a ratio between specific enzyme activities and citrate synthase serving as the control mitochondrial matrix enzyme.

Mitochondrial respiration was evaluated by both respiratory rate and respiratory control ratios (RCRs) using high resolution respirometry using (oxygraph) with Clark type oxygen electrodes (Fišar et al., 2016). Respiratory rate was determined as time derivation of oxygen concentration in the sample and RCRs was calculated as ratios of respiratory rates measured before and after substrates and/or inhibitors of OXPHOS.

3.4. Statistical methods

The study materials were statistically processed using the methods of parametric and nonparametric analysis in accordance with the results of testing the compared populations for normal distribution. Accumulation, corrections and systematization of the initial information and results visualization were performed in Microsoft Office Excel 2010.

271. Modica-Napolitano J.S., Lagace C.J. et al. Differential effects of typical and atypical neuroleptics on mitochondrial function in vitro. Arch Pharm Res 2003;26:951-9.
272. Moorhead T.W., McKirdy J. et al. Progressive gray matter loss in patients with bipolar disorder. Biol. Psychiatry 2007; 62: 894–900.
273. Moraes C.T., DiMauro S. et al. Mitochondrial DNA deletions in progressive external ophtalmoplegia and Kearns-Sayre syndrome. N Engl J Med. 1989 May 18;320(20):1293-9.
274. Moretti A.I., Gorini A., Villa R.F. Affective disorders, antidepressant drugs and brain metabolism. Mol Psychiatry. 2003 Sep;8(9):773-85.
275. Morris G., Berk M. The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. BMC Med. 2015; 13: 68.
276. Morris G., Walder K. et al. A model of the mitochondrial basis of bipolar disorder. Neurosci and Biobehav Rev. 2017. Vol 74 Part A: 1-20.
277. Moylan S., Berk M. et al. Oxidative & nitrosative stress in depression: why so much stress? J Psychiatr Res. 2014 Mar; 50: 36–41.
278. Munakata K., Iwamoto K. et al. Mitochondrial DNA 3243A>G mutation and increased expression of LARS2 gene in the brains of patients with bipolar disorder and schizophrenia. Biol Psychiatry. 2005;57:525–532.
279. Munakata K., Tanaka M. et al. Mitochondrial DNA 3644T-->C mutation associated with bipolar disorder. Genomics. 2004;84:1041–1050.
280. Munnich A., Rotig A. et al. Clinical presentation of mitochondrial disorders in childhood. J Inherit Metab Dis 19: (1996) 521-527.
281. Naydenov A.V., MacDonald M.L. et al. Differences in lymphocyte electron transport gene expression levels between subjects with bipolar disorder and normal controls in response to glucose deprivation stress. Arch Gen Psychiatry. 2007 May; 64(5):555-64.

261. Maurer I.C., Schippel P., Volz H.P. Lithium-induced enhancement mitochondrial oxidative phosphorylation in human brain tissue. Bipolar Disord. 2009;11:515–522.
262. Mayberg H.S. Modulating dysfunctional limbic–cortical circuits in depression: Towards development of brain-based algorithms for diagnosis and optimised treatment. Br. Med. Bull. 2003; 65: 193–207.
263. McBride H.M., Neuspiel M., Wasiak S. Mitochondria: more than just a powerhouse. Curr Biol. 2006;16:R551–560.
264. McMahon F.J., Chen Y.S. et al. Mitochondrial DNA sequence diversity in bipolar affective disorder. Am J Psychiat 2000; 157: 1058—1064.
265. Meyer J.H., Ginovart N. et al. Elevated monoamine oxidase a levels in the brain: An explanation for the monoamine imbalance of major depression. Arch. Gen. Psychiatry 2006; 63: 1209–1216.
266. Meyer J.H., Wilson A.A. et al. Brain monoamine oxidase a binding in major depressive disorder: Relationship to selective serotonin reuptake inhibitor treatment, recovery, and recurrence. Arch. Gen. Psychiatry 2009; 66: 1304–1312.
267. Michael N., Erfurth A. et al.. Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex. Psychopharmacology (Berl) 2003; 168: 344−346.
268. Michaelis M., Suhan T. et al. Valproic acid induces extracellular signal-regulated kinase 1/2 activation and inhibits apoptosis in endothelial cells. Cell Death Differ. 2006;13:446–453.
269. Milanesi E., Hadar A. et al. Insulin-like growth factor 1 differentially affects lithium sensitivity of lymphoblastoid cell lines from lithium responder and non-responder bipolar disorder patients. J. Mol. Neurosci. 2015; 56: 681–687.
270. Miller F.D., Kaplan D.R. Signaling mechanisms underlying dendrite formation. Curr. Opin. Neurobiol. 2003; 13: 391–398.

The statistical analysis was performed using the IBM SPSS Statistics v.20 program.

Each of the comparable sets of quantitative data was evaluated for compliance with the standard normal distribution law using the Shapiro-Wilk test which is recommended when a number of subjects are less than 60. The data distribution histogram, asymmetry and kurtosis parameters were also taken into account.

If a normal distribution of quantitative data was confirmed, the obtained data was combined into a variation series, in which the arithmetic mean values (M) and the standard deviations (σ) were calculated. The analysis was performed using the parametrical statistics method.

If the quantitative data distribution was non normal, the obtained data was described using the median (Me) and the lower and upper quartiles (Q1 and Q3). The analysis was performed using the nonparametric statistics method.

To assess the statistical significance of the differences in the mean values of normally distributed populations, the Student t-test was calculated (1):

$$t = \frac{M_1 - M_2}{\sqrt{m_1^2 + m_2^2}}, \qquad (1)$$

where: M_1 and M_2 – compared averages, m_1 and m_2 – standard errors of the average values.

When comparing the average values calculated for dependent populations (for example, before treatment and after treatment values), the paired Student t-test was calculated (2):

$$t = \frac{\overline{X}_D - \mu_0}{\frac{s_D}{\sqrt{n}}}, \qquad (2)$$

where: X_D - the average, s_D - standard deviation of those differences, μ_0 - non-zero. The degree of freedom used is $n - 1$, where n represents the number of pairs.

The obtained values of Student t-test were compared with critical values. Differences were considered statistically significant at a significance level of $p<0.05$.

To compare independent sets of quantitative data with a non normal distribution the Mann-Whitney U test was used. First a single ranked series from both of the compared samples were formed, where elements were sorted according to the value increase. A smaller rank was attributed to a smaller value. Then a single ranked series was divided into two, consisting, respectively, of the first and second samples units. The rank amounts were counted separately for each of the series. The Mann-Whitney U test was calculated (3):

$$U = n_1 \cdot n_2 + \frac{n_x \cdot (n_x + 1)}{2} - T_x, \qquad (3)$$

where n_1 – number of elements in sample 1, n_2 –

250. Machado-Vieira R., Andreazza A.C. et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007 Jun 21; 421(1):33-6.
251. Machado-Vieira R., Gattaz W.F. et al. Oxidative stress in early stage of bipolar disorder and the association with response to lithium. J Psychiatr Res. 2014 Mar; 50: 36–41.
252. Machado-Vieira R., Manji H.K., Zarate C.A. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disord. 2009;11(Suppl. 2):92–109.
253. Maletic V., Raison C. Integrated neurobiology of bipolar disorder. Front. Psychiatry 2014; 5: 98.
254. Mancuso M., Zeviani M. et al. Redefining phenotypes associated with mitochondrial DNA single deletion. J Neurol. 2015 Mar 26. [Epub ahead of print]
255. Manji H.K., Bersudsky Yet al. Modulation of protein kinase C isozymes and substrates by lithium: the role of myo-inositol. Neuropsychopharmacology 1996; 15: 370−381.
256. Manji H.K., Kato T et al. Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci. 2012. 13, 293-307.
257. Mannella C.A. The relevance of mitochondrial membrane topology to mitochondrial function. Biochim Biophys Acta. 2006;1762:140–147.
258. Marchetti P., Castedo M., et al. Mitochondrial permeability transition is a central coordinating even of apoptosis. J.Exp.Med., 1996, v.184, p. 1155-1160.
259. Mattson M.P., Gleichmann M., Cheng A. Mitochondria in neuroplasticity and neurological disorders. Neuron. 2008;60:748-66.
260. Maurer I., Möller H.J. Inhibition of complex I by neuroleptics in normal human brain cortex parallels the extrapyramidal toxicity of neuroleptics. Mol Cell Biochem. 1997 Sep; 174(1-2):255-9.

240. López-Larson M.P., DelBello M.P. et al. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol. Psychiatry 2002; 52: 93–100.
241. Luis P.B., Ruiter J.P. et al. Valproic acid metabolites inhibit dihydrolipoyl dehydrogenase activity leading to impaired 2-oxoglutarate-driven oxidative phosphorylation. Biochim Biophys Acta. 2007 Sep; 1767(9):1126-33.
242. Luft R. Luft's disease revisited. Severe hypermetabolism of nonthyroid origin with a defect in the maintenance of mitochondrial respiratory control. Mt Sinai J Med. 1992 Mar;59(2):140-5.
243. Luft R. The development of mitochondrial medicine. Proc Natl Acad Sci USA. 1994;91:8731–8.
244. Luft R., Ikkos D. Et al. A case of severe hypermetabolism of monthyroid origin with a defect in the maintenance of mitochondrial respiratory control: a correlated clinical, biochemical, and morphological study. J. Clin. Ivest. 1962. 41, 1776–1804.
245. Lutsenko S., Cooper M.J. Localization of the Wilson's disease protein product to mitochondria. Proc Natl Acad Sci U S A. 1998;95:6004–9.
246. Ma Y., Fang F. et al. The study of mitochondrial A3243G mutation in different samples. Mitochondrion. 2009 (9), 139–143.
247. MacDonald M.L., Naydenov A. et al. Decrease in creatine kinase messenger RNA expression in the hippocampus and dorsolateral prefrontal cortex in bipolar disorder. Bipolar Disord. 2006;8:255–264.
248. Maceluch J.A., Niedziela M. The clinical diagnosis and molecular genetics of Kearns-Sayre syndrome: a complex mitochondrial encephalomyopathy. Pediatr. Endocrinol. Rev. 2006. 4, 117–137.
249. Machado-Vieira R, Henter ID, Zarate CA, Jr. New targets for rapid antidepressant action. Prog. Neurobiol. 2015. doi: 10.1016/j.pneurobio.2015.12.001

number of elements in sample 2, n_x – number of elements in the bigger sample, and T_x – ranks sum for the bigger sample.

The calculated Mann-Whitney U test values were assessed by comparing them with the critical values: whether the calculated value was less or equal to the critical one, the statistical significance of the differences was accepted.

To assess the differences between two compared pairs of samples with a non normal distribution the Wilcoxon W-test was used. The change value was calculated for each patient. All the changes were ordered according to the absolute value. Then the signs of change ("+" or "-") were assigned to ranks and the ranks were summed up for each sign. The smaller rank amount (W) was compared to the W test critical value: whether the calculated value was less or equal to the critical one, the statistical significance of the differences was accepted.

To compare several groups of the patients (more than 2), a one-way analysis of variance was used. To assess the statistical significance of the differences the Fisher F test was calculated (4):

$$F = \frac{Q_1 /(m-1)}{Q_2 /(n-m)} \qquad (4)$$

where Q_1 – sum of the sample means to overall average squared deviations, Q_2 – sum of the observed values squared deviations, n – number of the elements, and m – number of the samples.

If the calculated value of Fisher's F test was less than critical, we made the conclusion that there was no statistically significant effect of the studied factor on the mean values of the trait. If the calculated value of Fisher's F test was larger than critical, the significant influence of the independent factor on the mean values for a certain level of statistical significance was recognized.

If statistically significant differences between groups existed, an additional pair comparison of the populations using the a posteriori criterion of Scheffe was carried out. To check the tightness of the relationship of the quantitative indicators the linear correlation coefficient rxy of Pearson was calculated (5):

$$r_{xy} = \frac{\sum(x-\bar{x})(y-\bar{y})}{\sqrt{\sum(x-\bar{x})^2 \cdot \sum(y-\bar{y})^2}} \quad (5)$$

To evaluate the quality of the linear function selection, the square of the linear correlation coefficient R^2 (the coefficient of determination) was calculated. The coefficient of determination shows the percent of factors considered in the model.

For the evaluation of the statistical significance of the correlation coefficient t-test was calculated (6):

228. Lan M.J., McLoughlin G.A. et al. Metabonomic analysis identifies molecular changes associated with the pathophysiology and drug treatment of bipolar disorder. Mol. Psychiatry 2009; 14: 269–279.
229. Lee B.H., Kim Y.K. Increased plasma VEGF levels in major depressive or manic episodes in patients with mood disorders. J. Affect. Disord. 2012; 136: 181–184.
230. Lener M.S., Niciu M.J. et al. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. Biol. Psychiatry 2016. doi: 10.1016/j.biopsych.2016.05.005
231. Licznerski P., Duman R.S. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. Neuroscience 2013; 251: 33–50.
232. Lightowlers R.N., Chinnery P.F. et al. 1997. Mammalian mitochondrial genetics: heredity, heteroplasmy and disease. Trends Genet. 13, 450–455.
233. Lin P.Y. State-dependent decrease in levels of brainderived neurotrophic factor in bipolar disorder: A metaanalytic study. Neurosci. Lett. 2009; 466: 139–143.
234. Liu X., Kim N.S. et al. Induction of apoptotic program in cell-free extracts: requirement for ATP and citochrom c , Cell, 1996, v. 86, p. 147-157.
235.
236. Logan D.C. The mitochondrial compartment. J Exp Bot. 2006;57:1225–1243.
237. Lombes A.I., Bonilla E., Dimauro S. Mitochondrial encephalomyopathies. Rev Neurol (Paris). 1989;145(10):671-89.
238. Lopez L.C., Luna-Sanchez M. et al. Pathomechanisms in coenzyme q10-deficient human fibroblasts. Mol. Syndromol., 5 (2014), pp. 163–169.
239. López-Gallardo E., López-Pérez M.J. et al. CPEO and KSS differ in the percentage and location of the mtDNA deletion. Mitochondrion. 2009. 9, 314–317.

216. Konradi C., Eaton M. et al. Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch Gen Psychiatry 2004;61:300-8.
217. Koopman W.J., Verkaart S. et al. Inhibition of complex I of the electron transport chain causes O2-. -mediated mitochondrial outgrowth. Am J Physiol Cell Physiol. 2005;288:C1440–C1450.
218. Koopman W.J., Willems P.H., Smeitink J.A. Monogenic mitochondrial disorders. N Engl J Med. 2012;366:1132–41.
219. Kostrouchová M., Kostrouch Z. et al. Valproic acid, a molecular lead to multiple regulatory pathways. Folia Biol (Praha). 2007;53(2):37-49.
220. Kowaltovski A.J., Castilho R.F., Vercesi A.E. Mitochondrial permeability transition and oxidative stress. FEBS Lett. 2001;495:12–15.
221. Krebs H.A., Weitzman P.D.J. Krebs' citric acid cycle: half a century and still turning. London: Biochemical Society. 1987.
222. Krishnan K.J., Reeve A.K. et al. What causes mitochondrial DNA deletions in human cells? Nat. Genet. 2008 Mar;40(3):275-9.
223. Kroll J.L. New directions in the conceptualization of psychotic disorders. Curr Opin Psychiatry. 2007;20:573–577.
224. Ku H.H., Brunk U.T., Sohal R.S. Relationship between mitochondrial superoxide and hydrogen peroxide production and longevity of mammalian species, Free Rad. Biol. Med., 1993, v.15, p. 621-627.
225. Kusumi I., Koyama T., Yamashita I. Thrombin-induced platelet calcium mobilization is enhanced in bipolar disorders. Biol Psychiatry. 1992;32:731–734.
226. Kyle U.G., Pichard C. The Dutch Famine of 1944-1945: a pathophysiological model of long-term consequences of wasting disease. Curr Opin Clin Nutr Metab Care. 2006;9:388–394.
227. Lai J.S., Zhao C. et al. Cytoprotection by lithium and valproate varies between cell types and cellular stresses. Eur J Pharmacol. 2006 Jun 6; 539(1-2):18-26.

$$t_r = \frac{r_{xy}}{\sqrt{1 - r_{xy}^2}} \cdot \sqrt{n-2} \qquad (6)$$

The obtained value was compared with the critical value for a certain level of significance and the number of degrees of freedom n-2. If the calculated value of t_r was larger than $t_{crit,}$ a certain level of statistical significance was recognized.

The values of the correlation coefficient were interpreted in accordance with the Chaddock scale (Tab. 1)

Tab. 1. The determination of the closeness of the correlation relationships, Chaddock scale

Coefficient	Quality characteristic
<0,1	no relationships
0,1 – 0,3	weak
0,3 – 0,5	moderate
0,5 – 0,7	salient
0,7 – 0,9	high
0,9 – 0,99	very high

To assess the dependence of one quantitative parameter to others, the linear regression method was used, and the reduced equation of the following kind was given (7):

$$y = a_0 + a_1x_1 + \ldots + a_nx_n, \qquad (7)$$

where y – quantitative trait, $x_1 \ldots x_n$ – factor traits, a_0 – constant, $a_1 \ldots a_n$– regression coefficients, showing the average change in the result y with a change in the factor x by one unit.

The obtained regression model allows us to calculate the theoretical values of the effective sign y from the given values of the factor x.

To compare the nominal scale values Pearson χ^2 test was used. It allows us to assess the significance of the differences between the actual number of outcomes or qualitative characteristics of a sample falling into each category, and the theoretical amount that can be expected in the study groups when a null hypothesis is valid.

First, the expected number of observations in each of the cells of the conjugacy table was calculated, provided that the null hypothesis of the absence of an interrelation was valid. For this purpose, the sums of rows and columns (marginal totals) were multiplied with the subsequent division of the obtained product by the total number of observations.

Then the value of the χ^2 was calculated (8):

$$\chi^2 = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{(O_{ij} - E_{ij})^2}{E_{ij}} \qquad (8)$$

where i – the row number (from 1 to r), j – the column number (from 1 to c) O_{ij} – actual number of observations in the cell ij, and E_{ij} – the expected number of observations in the cell ij.

205. Khairova R., Pawar R. et al. Effects of lithium on oxidative stress parameters in healthy subjects. Mol Med Rep. 2012;5:680–2.
206. Kiejna A., DiMauro S. et al. Psychiatric symptoms in a patient with the clinical features of MELAS. Med Sci Monit 2002; 8: CS66—CS72.
207. Kikuchi K., Iga J. et al. Lithium decreases VEGF mRNA expression in leukocytes of healthy subjects and patients with bipolar disorder. Hum. Psychopharmacol. 2011; 26: 358–363.
208. Kim H.K., Andreazza A.C. et al. Oxidation and nitration in dopaminergic areas of the prefrontal cortex from patients with bipolar disorder and schizophrenia. J Psychiatry Neurosci. 2014 Jul; 39(4): 276–285.
209. Kim H.W., Rapoport S.I., Rao J.S. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol. Dis. 2010; 37: 596–603.
210. Kim S., Choi K.H. et al. Suicide candidate genes associated with bipolar disorder and schizophrenia: an exploratory gene expression profiling analysis of post-mortem prefrontal cortex. BMC Genomics. 2007 Nov 12;8:413.
211. Kim Y.K., Na K.S. et al. High insulin-like growth factor-1 in patients with bipolar I disorder: A trait marker? J. Affect. Disord. 2013; 151: 738–743.
212. Kirk R., Furlong RA. et al. Mitochondrial genetic analyses suggest selection against maternal lineages in bipolar affective disorder. Am J Hum Genet 1999; 65: 508—518.
213. Klein A.B., Williamson R. et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int. J. Neuropsychopharmacol. 2011; 14: 347–353.
214. Kmiec B., Woloszynska M., Janska H. Heteroplasmy as a common state of mitochondrial genetic information in plants and animals. Curr. Genet. 2006. 50, 149–159.
215. Knapton S. 'Three-parent babies' could be born in Britain next year. The Daily Telegraph Science News, 1 March 2014.

195. Kato T., Murashita J. et al. Effect of photic stimulation on energy metabolism in the human brain measured by ^{31}P-MR spectroscopy. J Neuropsychiatry Clin Neurosci 1996; 8: 417−422.
196. Kato T., Shioiri T. et al. Lateralized abnormality of high energy phosphate metabolism in the frontal lobes of patients with bipolar disorder detected by phase-encoded ^{31}P-MRS. Psychol Med 1995; 25: 557−566.
197. Kato T., Stine O.C. et al. Increased levels of a mitochondrial DNA deletion in the brain of patients with bipolar disorder. Biol Psychiatry. 1997;42:871–875.
198. Kato T., Takahashi S. et al. Alterations in brain phosphorous metabolism in bipolar disorder detected by in vivo ^{31}P and ^{7}Li magnetic resonance spectroscopy. J Affect Disord 1993; 27: 53−59.
199. Kato T., Winokur G. et al. Quantitative analysis of leukocyte mitochondrial DNA deletion in affective disorders. Biol Psychiat 1997; 42: 311—316.
200. Kaukonen J.A., Zeviani M. et al. An autosomal locus predisposing to multiple deletions of mtDNA on chromosome 3p. Am J Hum Genet. 1996 Apr;58(4):763-9.
201. Kazuno A.A., Munakata K. et al. Mitochondrial DNA-dependent effects of valproate on mitochondrial calcium levels in transmitochondrial cybrids. Int J Neuropsychopharmacol. 2008;11:71–78.
202. Kearns T.P., Sayre G.P. Retinitis pigmentosa, external ophthalmoplegia and complete heart block. Archives Ophthalmology 1958 (60): 280-289.
203. Keller B.J., Yamanaka H., Thurman R.G. Inhibition of mitochondrial respiration and oxygen-dependent hepatotoxicity by six structurally dissimilar peroxisomal proliferating agents. Toxicology 1992;71:49-61.
204. Kempton M.J., Geddes J.R. et al. Meta-analysis, database, and metaregression of 98 structural imaging studies in bipolar disorder. Arch. Gen. Psychiatry 2008; 65: 1017–1032.

Then the value of the Pearson χ^2 test was compared to the critical values for (r-1) × (c-1) number of degrees of freedom. If the obtained value was larger than critical, a certain level of statistical significance was recognized and a statistical relationship between the studied risk factor and the outcome was confirmed.

For the four-field table analysis, when the number of expected observations in any of the cells of the four-field table was less than 10, the χ^2 test with the Yates correction was calculated. It reduces the risk of the first type error, i.e., detection of non-existent differences. The Yeats correction includes subtracting 0.5 from the absolute value of the difference between the actual and expected number of observations in each cell, which leads to a decrease in the χ^2 test value (9):.

$$\chi^2 = \sum_{i=1}^{r}\sum_{j=1}^{c}\frac{(\left|O_{ij} - E_{ij}\right| - 0{,}5)^2}{E_{ij}} \qquad (9)$$

To estimate the significance of the differences when the number of expected observations in any of the cells of the four-field table was less than 5, an accurate Fisher P test was calculated (10):

$$P = \frac{(A+B)!(C+D)!(A+C)!(B+D)!}{A!\,B!\,C!\,D!\,N!}, \qquad (10)$$

where A, B, C, D – actual numbers of observations in the cells of the contingency table, N – total number of the participants, and ! – a factorial, equal to the multiplication of a number by a sequence of numbers, each of which is less than previous by 1.

An obtained value of Fisher's exact P test more than 0.05 indicated the absence of statistically significant differences. An obtained value of Fisher's exact P test less than 0.05 indicated their presence.

To compare the relative values characterizing the associated populations (at the beginning and at the end of the observation) the McNemar test was used. It is used to determine whether any changes in the distribution structure values of two dependent variables occur (11):

$$Q = \frac{(b-c)^2}{b+c} \qquad (11)$$

where Q – McNemar test, b – the number of patients with a negative result in the first observation and positive result in the second, and c – the number of patients with a positive result in the first observation and negative result in the second.

The McNemar test values were interpreted by comparison with critical values.

To identify factors that characterize the relationships between groups of characteristics and to reduce the number of analyzed variables, a four-stages factor analysis was used:

183. Kang D., Hamasaki N. Mitochondrial disease: maintenance of mitochondrial genome and molecular diagnostics. Adv Clin Chem. 2006;42:217-54.
184. Kaplan D.R., Miller F.D. Neurotrophin signal transduction in the nervous system. Curr. Opin. Neurobiol. 2000; 10: 381–391.
185. Karamustafalioglu N., Genc A. et al. Plasma BDNFs level initially and post treatment in acute mania: Comparison between ECT and atypical antipsychotic treatment and healthy controls. J. Psychopharmacol. 2015; 29: 898–902.
186. Kato T. Mitochondrial dysfunction as the molecular basis of bipolar disorder: therapeutic implications. CNS Drugs. 2007;21(1):1-11.
187. Kato T. Mitochondrial dysfunction contribution to bipolar disorder confirmed using model mice (Riken). Molecular Psychiatry, 2006: 11, 965–978.
188. Kato T. Mitochondrial dysfunction in bipolar disorder. Nihon Shinkei Seishin Yakurigaku Zasshi. 2005 Apr; 25(2): 61-72.
189. Kato T. Role of mitochondrial DNA in calcium signaling abnormality in bipolar disorder. Cell Calcium 2008;44(1): 92-102.
190. Kato T. The other, forgotten genome: mitochondrial DNA and mental disorders. Mol Psychiat 2001; 6: 625—633.
191. Kato T., Ishiwata M. et al. Mechanisms of altered Ca2+ signalling in transformed lymphoblastoid cells from patients with bipolar disorder. Internat J of Psychopharmacol. 6(4) 379-389.Kato T., Kato N. Mitochondrial dysfunction in bipolar disorder. Bipolar Disord 2000;2:180-90.Kato T., Kunugi H. et al. Association of bipolar disorder with the 5178 polymorphism in mitochondrial DNA. Am J Med Genet 2000; 96: 182−186.
194. Kato T., Murashita J. et al. Decreased brain intracellular pH measured by ^{31}P-MRS in bipolar disorder: a confirmation in drug-free patients and correlation with white matter hyperintensity. Eur Arch Psychiatry Clin Neurosci 1998; 248: 301−306.

mitochondrial ultrastructure of white blood cells in patients diagnosed as schizophrenia and treated with antipsychotic drugs. Biotech Histochem 2005;80:133-7.
173. Iwamoto K., Bundo M. et al. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis.Hum Mol Genet. 2005 Jan 15; 14(2):241-53.
174. Jacobs W.B., Kaplan D.R., Miller F.D. The p53 family in nervous system development and disease. J. Neurochem. 2006; 97: 1571–1584.
175. Jenuth J.P., Peterson A.C. et al. Random genetic drift in the female germline explains the rapid segregation of mammalian mitochondrial DNA. Nat Genet 1996; 14: 146–51.
176. Johns D.R., Neufeld M.J. Cytochrome b mutations in Leber hereditary optic neuropathy. Biochem. Biophys. Res. Commun. 1991.181, 1358–1364.
177. Jones D.M., Tucker B.A. et al. The synergistic effects of NGF and IGF-1 on neurite growth in adult sensory neurons: Convergence on the PI 3- kinase signaling pathway. J. Neurochem. 2003; 86: 1116–1128.
178. Jones R.C. Buchanan B.B., Gruissem W. Biochemistry & molecular biology of plants. 1st ed. Rockville, Md: American Society of Plant Physiologists. 2000.
179. Jope R.S., Roh M.-S. Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. Curr Drug Targets 2006;7:1421-34.
180. Jou S.H., Chiu N.Y., Liu C.S. Mitochondrial dysfunction and psychiatric disorders. Chang Gung Med J. 2009 Jul-Aug;32(4):370-9.
181. Jun C., Choi Y. et al. Disturbance of the glutamatergic system in mood disorders. Exp. Neurobiol. 2014; 23: 28–35.
182. Kanabus M., Heales S.J., Rahman S. Development of pharmacological strategies for mitochondrial disorders. Br. J. Pharmacol., 171 (2014), pp. 1798–1817.

1) calculation of the correlation matrix for all variables participating in the analysis;

2) extraction of factors by the principal component method;

3) the rotation of factors to create a simplified structure using Varimax method;

4) analysis of factor loads matrix and the interpretation of factors.

4. Výsledky

4.1. Clinical evaluation of the BPD patients in manic or depressive episode

All the subjects were divided into 2 groups: experimental group (37 patients with BPD) and control group (21 healthy individuals). The experimental group, in turn, consisted of 24 patients in manic episode of the disease (subgroup A) and 13 patients in depressive episode of the disease (subgroup B). Clinical evaluation and biochemical measurement of BAD in-patients were done both at the beginning of treatment and when released from hospital treatment (in remission or partial remission). The average age within groups is shown in Table 1.

Tab. 1. Age structure in the experimental group (patients with bipolar disorder) and control group

Group	Subgroup	Age (years)		N
		min-max	M±SD	
Experimental	- All	21 – 65	42.2±12.2	37
	- Subgroup A	21 – 65	39.5±13.2	24
	- Subgroup B	30 – 59	46.9±8.7	13
Control		25 – 61	40.3±10.3	21

Subgroup A = manic episode; Subgroup B = depressive episode

A one-way analysis of variance (ANOVA) did not show a statistically significant difference in age between control

161. Hibar D.P., Westlye L.T. et al. Subcortical volumetric abnormalities in bipolar disorder. Mol. Psychiatry 2016; 21: 1710–1716.
162. Hillhouse T.M., Porter J.H. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Exp. Clin. Psychopharmacol. 2015; 23: 1–21.
163. Hirschfeld R.M., Williams J.B. et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry. 2000 Nov; 157(11):1873-5.
164. Holt I.J., Harding A.E., Morgan-Hughes J.A. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature. 1988 Feb 25;331(6158):717-9.
165. Holt I.J., Lorimer H.E., Jacobs H.T. Coupled leading- and lagging-strand synthesis of mammalian mitochondrial DNA. Cell 2000; 100: 515–24.
166. Hroudova J., Fisar Z. Connectivity between mitochondrial functions and psychiatric disorders. Psych and Clin Neurosci. 2011.Vol 65, Iss 2: 130-141.
167. Hroudová J., Fišar Z. In vitro inhibition of mitochondrial respiratory rate by antidepressants. Toxicol Lett. 2012;213:345-52.
168. Hutchison C.A. 3rd, Newbold J.E. et al. Maternal inheritance of mammalian mitochondrial DNA. Nature. 1974 Oct 11;251(5475):536-8.
169. Hwang J., Zheng L.T. et al. Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. Neuropharmacology. 2008;55:826-34.
170. Ichas F., Jouaville L.S., Mazai J.P. Mitochondria are excitable organelles capable of generation and converting electrical and calcium signals. Cell, 1997, v. 89, p.1145-1153.
171. Inagaki T., Ishino H. et al. Psychiatric symptoms in a patient with diabetes mellitus associated with point mutation in mitochondrial DNA. Biol Psychiat 1997; 42: 1067—1069.
172. Inuwa I.M., Peet M., Williams M.A. QSAR modeling and transmission electron microscopy stereology of altered

150. Hamakawa H., Murashita J. et al. Reduced intracellular pH in the basal ganglia and whole brain measured by ^{31}P-MRS in bipolar disorder. Psychiatry Clin Neurosci 2004;58:82-8.
151. Hamon M., Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. Prog. Neuropsychopharmacol. Biol. Psychiatry 2013; 45: 54–63.
152. Harman D. A biologic clock: the mitochondria?. Journal of the American Geriatrics Society, 1972, 20(4): 145-147.
153. Harman D. Free radical theory of aging: Consequences of mitochondrial aging, Age, 1983, 6: 86-94.
154. Harrisberger F., Smieskova R. et al. BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2015; 55: 107–118.
155. Harro J., Kanarik M. et al. Revealing the cerebral regions and networks mediating vulnerability to depression: oxidative metabolism mapping of rat brain. Behav Brain Res. 2014 Jul 1;267:83-94.
156. Harwood A.J. Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. Mol Psychiatry. 2005 Jan;10(1):117-26.
157. Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: An historical overview and future directions. Psychiatry Clin. Neurosci. 2010; 64: 341–357.
158. Heninger G.R., Delgado P.L., Charney D.S. The revised monoamine theory of depression: A modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 1996; 29: 2–11.
159. Hermann G.J., Thatcher J.W. et al. Mitochondrial fusion in yeast requires the transmembrane GTPase Fzo1p. J Cell Biol. 1998;143:359–373.
160. Herrero A., Baria G. Localization of the site of oxygen radical generation inside the mitochondria, J. Bioenerg. Biomembr., 2000, v. 32, p.609-615.

group and experimental groups (all p=0.565, subgroup A p=0.156, and subgroup B p=0.147); it proves that groups are age-matched and no correction for age is necessary in data analysis.

First stage of the research included the assessment of the mental state of the patients with BPD. The following tests were used for patients in the manic episode: Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMRS), Mood Disorder Questionnaire (MDQ). Tests for patients in the depressive episode included: BPRS, Montgomery-Asberg Depression Rating Scale (MADRS), MDQ. For patients in remission we added Clinical Global Impression – Improvement scale (CGI-I) to measure the clinical improvement. (Tab. 2)

Tab. 2. Mental state assessment in the experimental group at the beginning of treatment and when released from treatment (measurements 1 and 2)

Test method	Episode	State of the patient		p
		Disease (acute state), measurement 1	Remission, measurement 2	
BPRS	Depressive	55 (44.5-68.5)	30 (27-33)	<0.001
	Manic	51.5 (41.5-66.5)	33 (29-41.5)	0.018
	p	0.952	0.177	-
MADRS	Depressive	26.5 (19-31)	4 (0-4)	<0.001
YMRS	Manic	20 (13.5-26)	1.5 (0-5)	<0.001
CGI-I		-	xx	

Mean (range); p – significance level

Data obtained from the Wilcoxon-Mann-Whitney test shows that the difference between the BPRS test scores in the acute state of the disease and in remission was significant within both A ($p<0.001$) and B ($p=0.018$) subgroups. In patients with mania the median BPRS score decreased from 51.5 to 33 and in patients with depression it decreased from 55 to 30. The decrease was comparable in both the subgroups. The difference in BPRS test scores between patients with mania and patients with depression were not significant in either the acute phase of the disease ($p=0.952$) or in remission ($p=0.177$) (Fig. 1).

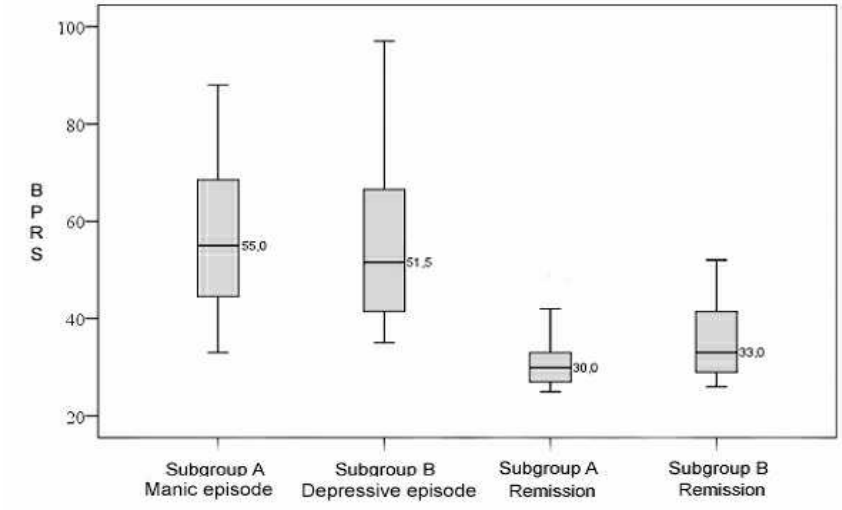

Fig. 1. BPRS test score in patients with mania and depression at the beginning and at the end of the study. Subgroup A = manic episode, Subgroup B = depressive episode. BPRS – Brief Psychiatric Rating Scale

140. Gilkerson R.W. Mitochondrial DNA nucleoids determine mitochondrial genetics and dysfunction. Int. J. Biochem. Cell Biol. 2009.41, 1899–1906.
141. Goncalves C.L., Rezin G.T. et al. Differential effects of escitalopram administration on cortical and subcortical brain regions metabolic parameters of Wistar rats. Acta Neuropsychiatr. 2012;24:147-54.
142. Gould T.D., Chen G., Manji H.K. Mood stabilizer psychopharmacology. Clin. Neurosci. Res. 2002; 2: 193–212.
143. Gould T.D., Picchini A.M. et al. Targeting glycogen synthase kinase-3 in the CNS: Implications for the development of new treatments for mood disorders. Curr. Drug Targets 2006; 7: 1399–1409.
144. Grande I., Fries G.R. et al. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Invest. 2010; 7: 243–250.
145. Grover S., Padhy S.K. et al. Mania as a first presentation in mitochondrial myopathy. Psychiatry Clin Neurosci. 2006;60:774–775.
146. Gubert C., Stertz L. et al. Mitochondrial activity and oxidative stress markers in peripheral blood mononuclear cells of patients with bipolar disorder, schizophrenia, and healthy subjects. J Psychiatr Res. 2013 Oct;47(10):1396-402.
147. Gupta A., Schulze T.G. et al. Interaction networks of lithium and valproate molecular targets reveal a striking enrichment of apoptosis functional clusters and neurotrophin signaling. Pharmacogenomics J. 2012 Aug; 12(4):328-41.
148. Hajek T., Bauer M. et al. Large positive effect of lithium on prefrontal cortex N-acetylaspartate in patients with bipolar disorder: 2-centre study. J Psychiatry Neurosci. 2012 May; 37(3):185-92.
149. Hamakawa H., Kato T. et al. Quantitative proton magnetic resonance spectroscopy of the bilateral frontal lobes in patients with bipolar disorder. Psychol Med 1999; 29: 639−644.

130. Forlenza M., Miller E. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. Psychosom Med 2006;68:1-7.
131. Fox T.D. Mitochondrial protein synthesis, import, and assembly. Genetics. 2012 Dec;192(4):1203-34.
132. Freitas T.P., Rezin G.T. et al. Evaluation of citrate synthase activity in brain of rats submitted to an animal model of mania induced by ouabain. Mol. Cell. Biochem. 2010, 341. pp. 245-249.
133. Frey B.N., Stanley J.A. et al. Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an in vivo 1H MRS study. Bipolar Disord. 2007;9(Suppl 1):119–127.
134. Gardner A., Johansson A. et al. Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients. J Affect Disord. 2003 Sep;76(1-3):55-68.
135. Gardner A., Pagani M. et al. Alterations of rcbf and mitochondrial dysfunction in major depressive disorder: a case report. Acta Psychiat Scand 2003; 107: 233—239.
136. Gass P., Riva M.A. CREB, neurogenesis and depression. Bioessays 2007; 29: 957–961.
137. Gavin D.P., Kartan S. et al. Histone deacetylase inhibitors and candidate gene expression: An in vivo and in vitro approach to studying chromatin remodeling in a clinical population. J Psychiatr Res. 2009;43:870–876.
138. Gerhard D.M., Wohleb E.S., Duman R.S. Emerging treatment mechanisms for depression: Focus on glutamate and synaptic plasticity. Drug Discov. Today 2016; 21: 454–464.
139. Gigante A.D., Bond D.J. et al. Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: A meta-analysis. Bipolar Disord. 2012; 14: 478–487.

The Wilcoxon-Mann-Whitney test was also applied to establish the difference between the MADRS test score in the acute state of the disease and in remission. The decrease after treatment was significant ($p<0.001$). The median MADRS assessment decreased from 26.5 to 4 (Fig. 2).

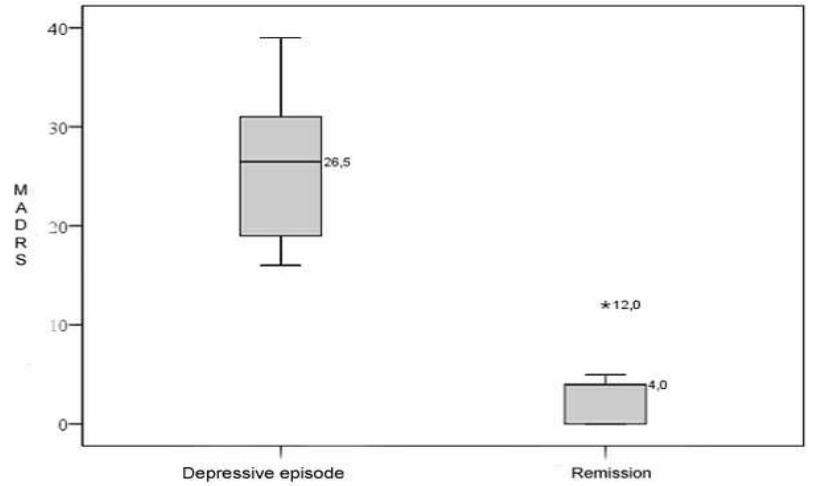

Fig. 2. MADRS test results in patients with depression at the beginning and at the end of the study

A significant decrease in the YMRS test score between patients in the manic episode and patients in remission was also established ($p<0.001$). The median in the acute phase was 20, in remission it decreased to 1.5. (Fig. 3)

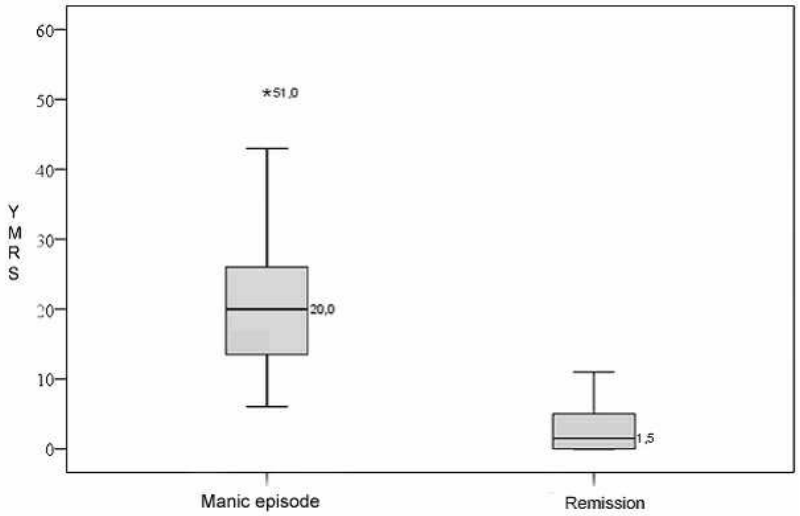

Fig. 3. YMRS test results in patients with mania and depression at the beginning and at the end of the study

The results of the CGI-I test were examined only at the end of the research as it is used to assess the quality of remission in mentally ill patients. (Tab. 3)

Tab. 3. CGI-I test results in patients with bipolar disorder in manic and depressive episode at the end of the study (remission)

CGI test	Subgroups				p
	A (mania)		B (depression)		
	Me	Q_1-Q_3	Me	Q_1-Q_3	
Scale I	2	1-2	2	1-3	0.694
Scale II	2	1-2	2	1-2	0.885
Scale III	41	41-42	41	31,5-41,5	0.462

p – significance level; Me = mean range; Q_1- Quartile 1, Q_3 - Quartile 3.

potential adjunctive tool for differential diagnosis. J. Psychiatr. Res. 2009; 43: 1200–1204.
119. Fernandes B.S., Gama C.S. et al. Increased neurotrophin-3 in drug-free subjects with bipolar disorder during manic and depressive episodes. J. Psychiatr. Res. 2010; 44: 561–565.
120. Fernandes B.S., Molendijk M.L. et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: A meta-analysis of 52 studies. BMC Med. 2015; 13: 289.
121. Ferreira G.K., Cardoso M.R. et al. Fluvoxamine alters the activity of energy metabolism enzymes in the brain. Rev Bras Psiquiatr. 2014 Sep;36(3):220-6.
122. Filipek P.A., Juranek J. et al. Mitochondrial disfunction in autistic patients with 15q inverted duplication. Ann Neurol 2003; 53: 801—804.
123. Finsterer J. Genetic, pathogenetic, and phenotypic implications of the mitochondrial A3243G tRNALeu (UUR) mutation. Acta Neurol. Scand. 2007 (116), 1–14.
124. Finsterer J. Hematological manifestations of primary mitochondrial disorders. Acta Haematol. 2007. 118: 88–98.
125. Finsterer J. Treatment of mitochondrial disorders. Eur. J. Paediatr. Neurol. 2010. 14, 29–44.
126. Fišar Z, Hroudová J. Intracellular signalling pathways and mood disorders. Folia Biol. (Praha) 2010; 56: 135–148.
127. Fišar Z. Drugs related to monoamine oxidase activity. Prog. Neuropsychopharmacol. Biol. Psychiatry 2016; 69: 112–124.
128. Fišar Z. Pathophysiology of mood disorders and mechanisms of action of antidepressants and mood stabilizers. In: Van Bockstaele EJ (ed.). Endocannabinoid Regulation of Monoamines in Psychiatric and Neurological Disorders. Springer, New York, 2013; 103–134.
129. Fisar Z., Hroudova J. et al. Mitochondrial respiration in patients with Alzheimer's disease. Curr Alzheimer Res 2016.13: 930-41.

107. Erecinska M., Silver I.A. ATP and brain function. J Cereb Blood Flow Metab 1989; 9: 2−19.
108. Erkan O.M., Gulec M. et al. Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clinl Psychopharmacol 2004;19:89-95.
109. Ernster L., Ikkos D., Luft R. Enzymic activities of human skeletal muscle mitochondria: a tool in clinical metabolic research. Nature. 1959. 184, 1851–1854.
110. Escobar-Henriques M., Langer T. Mitochondrial shaping cuts. Biochim Biophys Acta. 2006;1763:422–429.
111. Facts about genetics and neuromuscular diseases. Genetic and neuromuscular diseases. Muscular Dystrophy Association Inc. 2011.
112. Falkenberg M., Gaspari M. et al. Mitochondrial transcription factors B1 and B2 activate transcription of human mtDNA. Nat Genet 2002; 31: 289–94.
113. Fattal O., Budur K. Et al. Review of the literature on major mental disorders in adult patients with mitochondrial diseases. Psychosomatics 2006;47:1-7.
114. Feier G., Valvassori S.S. et al. Lithium and valproate modulate energy metabolism in an animal model of mania induced by methamphetamine. Pharmacol Biochem Behav. 2013 Jan;103(3):589-96.
115. Feldhaus P., Fraga D.B. et al. Evaluation of respiratory chain activity in lymphocytes of patients with Alzheimer disease. Metab Brain Dis,2011.26:229-36.
116. Fernandes B.S., Berk M. et al. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: A comparative meta-analysis. Mol. Psychiatry 2014; 19: 750–751.
117. Fernandes B.S., Gama C.S. et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: A systematic review and metaregression analysis. J. Psychiatr. Res. 2011; 45: 995–1004.
118. Fernandes B.S., Gama C.S. et al. Serum brain-derived neurotrophic factor in bipolar and unipolar depression: A

The Wilcoxon-Mann-Whitney test did not reveal a significant difference between the CGI-I test results in either A or B subgroups ($p>0.05$ for all CGI-I scales). Median assessments for the scales I, II, III were 2, 2, 41 respectively. We can summarize that there was no difference in the quality of clinical improvement between patients with bipolar disorder in a manic episode and patients with bipolar disorder in a depressive episode.

4.2. Mitochondrial functions in BPD patients and healthy controls

The second stage of the research consisted of the comparison of the mitochondrial function in patients with BPD (in acute manic or depressive episodes) and healthy controls.

Activities of mitochondrial enzymes, citrate synthase (CS), complexes I (CI), II (CII) and IV (COX) in patients with BPD are graphically presented in Fig. 4 and 5.

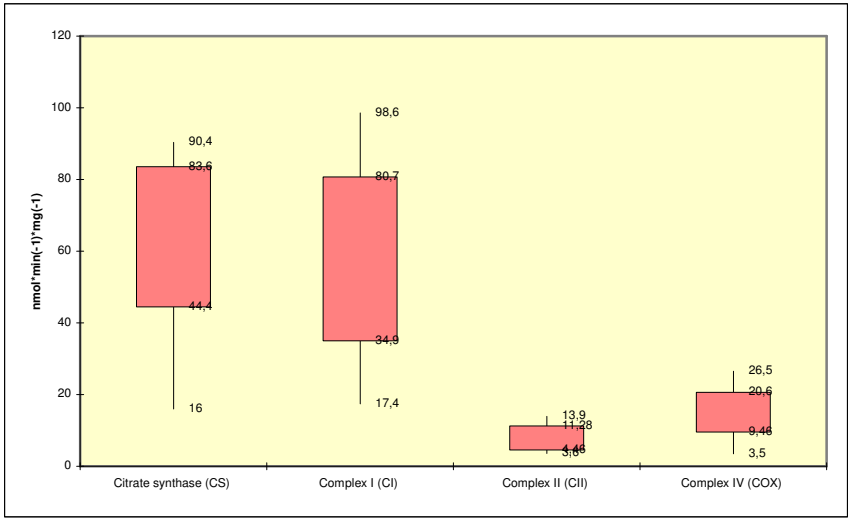

Fig. 4. Mitochondrial enzymes activity in the experimental group (patients with bipolar disorder in depressive episode, N=13). Min, Mean-SD, Mean+SD, Max, SD – standard deviation

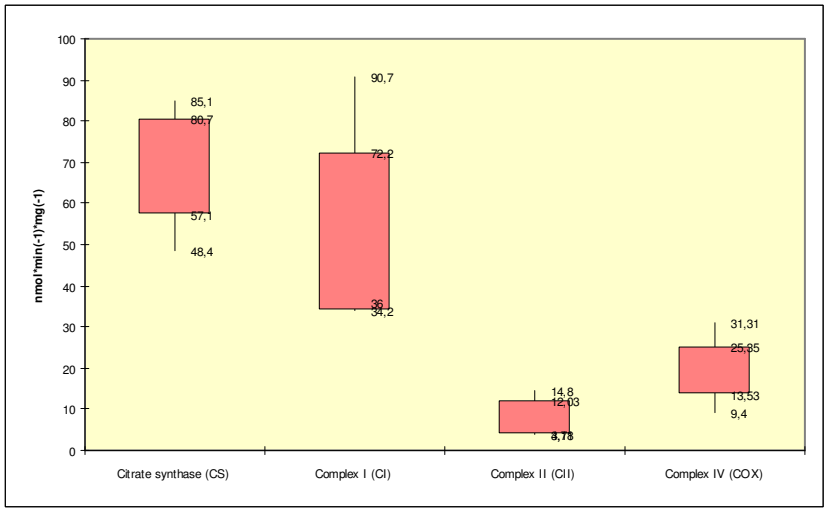

Fig. 5. Mitochondrial enzymes activity in the experimental group (patients with bipolar disorder in manic episode, N=24). Min, Mean-SD, Mean+SD, Max, SD – standard deviation

95. Duman R.S. Synaptic plasticity and mood disorders. Mol. Psychiatry 2002; 7 (Suppl. 1: S29–S34).
96. Dunlop B.W., Nemeroff C.B. The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 2007; 64: 327–337.
97. Duong A., Syed B., Scola G. Biomarkers for bipolar disorder: Current insights. Curr. Biomark. Find. 2015; 5: 79–92.
98. Duric V., Duman R.S. Depression and treatment response: Dynamic interplay of signaling pathways and altered neural processes. Cell. Mol. Life Sci. 2013; 70: 39–53.
99. Dykens J.A., Jamieson J.D. et al. In vitro assessment of mitochondrial dysfunction and cytotoxicity of nefazodone, trazodone, and buspirone. Toxicol Sci. 2008;103:335-45.
100. Easterday O.D., Featherstone R.M. et al. Blood glutathione, lactic acid and pyruvic acid relationshi ps in schizophrenia. AMA Arch Neurol Psychiat 1952; 68: 48—57.
101. Egger J., Wilson J. Mitochondrial inheritance in a mitochondrially mediated disease. N Engl J Med. 1983 Jul 21;309(3):142-6.
102. Einat H., Manji H.K. Cellular plasticity cascades: Genesto-behavior pathways in animal models of bipolar disorder. Biol. Psychiatry 2006; 59: 1160–1171.
103. Eleff S.M., Barker P.B. et al.. Phosphorus magnetic resonance spectroscopy of patients with mitochondrial cytopathies demonstrates decreased levels of brain phosphocreatine. Ann Neurol 1990; 27: 626−630.
104. Elliott H.R., Samuels D.C. et al. Pathogenic mitochondrial DNA mutations are common in the general population. Am. J. Hum. Genet. 2008. 83 (2): 254–60.
105. Engel A.G., Angelini C. Carnitine deficiency of human skeletal muscle with associated lipid storage myopathy: a new syndrome. Science. 1973 Mar 2;179(4076):899-902.
106. Engel W.K., Cunningham G.G. Rapid examination of muscle tissue. An improved trichrome method for fresh-frozen biopsy sections. Neurology 1963. Nov, 13. 919-923.

84. DiMauro S., Andreu A.L. Mutations in mtDNA: are we scraping the bottom of the barrel? Brain Pathol. 2000 Jul;10(3):431-41.
85. DiMauro S., DiMauro P.M. Muscle carnitine palmityltransferase deficiency and myoglobinuria. Science. 1973 Nov 20;182(4115):929-31.
86. DiMauro S., Hirano M. Pathogenesis and treatment of mitochondrial disorsers. Chapter 10 in 'Inherited neuromuscular diseases. Advances in experimental medicine and biology'. 2009, p. 140-162.
87. DiMauro S., Moraes C.T. Mitochondrial encephalomyopathies. Arch Neurol. 1993 Nov; 50(11):1197-208.
88. DiMauro S., Rustin P. A critical approach to the therapy of mitochondrial respiratory chain and oxidative phosphorylation diseases. Biochim. Biophys. Acta. 2009. 1792, 1159–1167.
89. Dimmer K.S., Rapaport D. Proteomic view of mitochondrial function. Genome Biol. 2008. 9, 209.
90. Drachman D.B. Ophthalmoplegia plus: the neurodegenerative disorders associated with peogressive external ophthalmoplegia. Archives of Neurology 1968 (18): 657 – 674.
91. Dror N., Klein E. et al. State-dependent alterations in mitochondrial complex I activity in platelets: a potential peripheral marker for schizophrenia. Mol Psychiatry. 2002; 7(9):995-1001.
92. Du C., Fang M. et al. S mac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP ingibition, Cell , 2000,v. 102, p. 33-42.
93. Dubovsky S.L., Murphy J. et al. Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. Am J Psychiatry. 1992;149:118–120.
94. Duman R.S., Heninger G.R., Nestler E.J. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 1997; 54: 597–606.

After the post-hoc Scheffe test was performed, significant differences were not found between any of mitochondrial enzymes activity in patients with mania and depression (Tab. 4). The mitochondrial enzymes activity data from the group of healthy controls was not available; reference ranges of mitochondrial enzyme activities were obtained from mitochondrial laboratory of the Department of Pediatrics and Adolescent Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague.

Tab. 4. Mitochondrial enzymes in patients with bipolar disorder in a manic or depressive episode

Mitochondrial enzyme	Group		p	Reference range
	Mania	Depression		
CS (nmol·min^{-1}·mg^{-1})	68.9±11.8	64.0±19.6	0.397	60-92
CI (nmol·min^{-1}·mg^{-1})	53.2±19.0	57.8±22.9	0.561	21-55
CII (nmol·min^{-1}·mg^{-1})	8.07±3.96	7.87±3.41	0.89	5-15
COX (nmol·min^{-1}·mg^{-1})	19.44±5.91	15.03±5.57	**0.054**	16-40

CS = citrate synthase; CI = Complex I; CII = Complex II; COX = Complex IV. Mean ± SD; p – significance level

Complex I (CI) activity in BPD patients with mania was lower than in patients with depression; Complex II (CII) activity in BPD patients with mania was higher than in patients

with depression; citrate synthase (CS) activity in BPD patients with mania was higher than in patients with depression, though none of the above had reached statistical significance. When comparing a decrease in Complex IV (COX) activity in BPD patients with depression with BPD patients with mania, the significance level was close to 0.05 (Fig. 6). Complex IV activity in BPD patients in depressive episode was slightly below reference range.

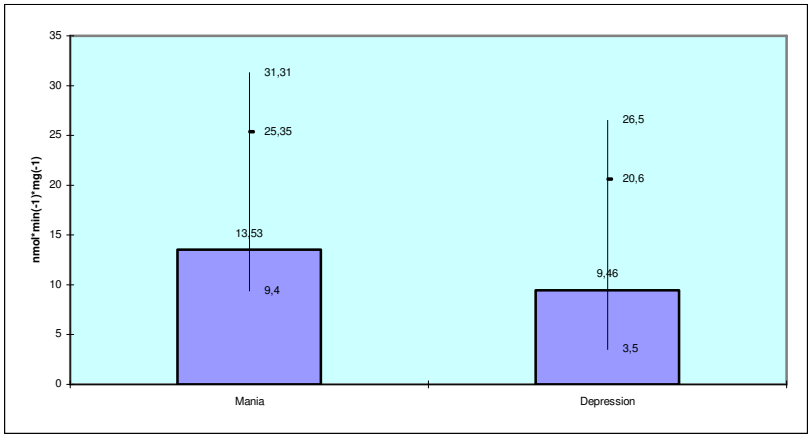

Fig. 6. Complex IV (COX) activity in patients with bipolar disorder in manic episode and depressive episode, p=0.054. Min, Mean-SD, Mean+SD, Max, where SD – standard deviation

Changes in mitochondrial respiration in the blood platelets isolated from patients with BPD and healthy controls were examined through the general linear model, one-way analysis of variance and post-hoc Scheffé test. The results are summarized in Tab. 5.

74. Crompton M. The mitochondrial permeability transition pore and its role in cell death. Biochem. 1999. J. 341, 233 – 249.
75. Cui J., Shao L. Et al. Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. Neuroscience 2007;144:1447-53.
76. Curti C., Mingatto F.E. et al. Fluoxetine interacts with the lipid bilayer of the inner membrane in isolated rat brain mitochondria, inhibiting electron transport and F1F0-ATPase activity. Mol Cell Biochem 1999;199:103-9.
77. Dager S.R., Friedman S.D. et al. Brain metabolic alterations in medication-free patients with bipolar disorder. Arch Gen Psychiatry 2004; 61: 450−458.
78. de Sousa R.T. et al. Lithium increases leukocyte mitochondrial complex I activity in bipolar disorder during depressive episodes. Psychopharmacology (Berl), 2015. Jan;232(1):245-50.
79. Dean C.E. Antipsychotic-associated neuronal changes in the brain: Toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:174–189.
80. Deicken R.F., Pegues M.P. et al. Lower concentration of hippocampal N-acetylaspartate in familial bipolar I disorder. Am J Psychiatry 2003; 160: 873−882.
81. Deicken R.F., Weiner M.W., Fein G. Decreased temporal lobe phospho-monoesters in bipolar disorder. J Affect Disord. 1995 Mar 14; 33(3):195-9.
82. Desnuelle C. et al. Mitochondrial DNA variations in patients with maternally inherited diabetes and deafness syndrome. Biochem. Biophys. Res. Commun. 2000. 3, 771–775.
83. Diehl N.L., Enslen H. et al. Activation of the p38 mitogen-activated protein kinase pathway arrests cell cycle progression and differentiation of immature thymocytesin vivo. J.Exp.Med., 2000, v.191, p. 324-334.

62. Chinnery P., Majamaa K. Et al. Treatment for mitochondrial disorders. Cochrane. Database. Syst. Rev. 1, 2000, CD004426.
63. Chinnery P.F. Mitochondrial Disorders Overview. GeneReviews® [Internet]. Initial Posting: June 8, 2000; Last Update: August 14, 2014.
64. Chinnery P.F., DiMauro S. et al. Risk of developing a mitochondrial DNA deletion disorder. Lancet. 2004. 364, 592–596.
65. Chiu C.T., Wang Z. Et al. Therapeutic Potential of Mood Stabilizers Lithium and Valproic Acid: Beyond Bipolar Disorder Pharmacol Rev. 2013 Jan; 65(1): 105–142.
66. Clark J.B. N-acetyl aspartate: a marker for neuronal loss or mitochondrial dysfunction. Dev Neurosci 1998; 20: 271−276.
67. Clausen T., Zauner A. et al. Induced mitochondrial failure in the feline brain: implications for understanding acute post-traumatic metabolic events. Brain Res 2001; 908: 35−48.
68. Clay H., Sillivan S., Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. Int J Dev Neurosci. 2011 May; 29(3):311-324.
69. Conte D., Narindrasorasak S., Sarkar B. In vivo and in vitro iron-replaced zinc finger generates free radicals and causes DNA damage. The Journal Of Biological Chemistry. 1996;271(9) 5125-30.
70. Coppen A. The biochemistry of affective disorders. Br. J. Psychiatry 1967; 113: 1237–1264.
71. Corena-McLeod M., Walss-Bass C. et al. New model of action for mood stabilizers: phosphoproteome from rat pre-frontal cortex synaptoneurosomal preparations. PLoS One. 2013 May 14;8(5):e52147.
72. Correa C., Amboni G. et al. Effects of lithium and valproate on hippocampus citrate synthase activity in an animal model of mania. Progress Neuropsychopharmacol. Biol. Psychiatry, 31 (2007), pp. 887-891.
73. Craddock N, Davé S, Greening J. Association studies of bipolar disorder. Bipolar Disord. 2001; 3: 284–298.

Tab 5. Mitochondrial respiration in the blood platelets from patients with bipolar disorder (measurement 1, manic or depressive episode) and healthy controls

Platelets	Respi-ratory state	Groups					
		Mania	P (Mania vs Controls)	Depression	P (Depression vs Controls)	Controls	P (Mania vs Depression)
Intact	PR	0.105±0.017	0.752	0.101±0.014	0.463	0.106±0.023	0.343
	LEAK	0.00656±0.00483	**0.005**	0.00534±0.00241	0.267	0.00169±0.00123	0.568
	ETSC	0.124±0.022	0.256	0.117±0.02	0.164	0.132±0.03	0.233
	Rotenone	0.00044±0.00036	0.148	-0.00151±0.00109	0.64	0.00164±0.00119	0.451
Permeabilized	IR (p)	0.087±0.021	0.32	0.082±0.026	0.24	0.094±0.021	0.678
	DMP (p)	0.046±0.028	0.188	0.034±0.014	0.564	0.038±0.014	0.355
	ADP (p)	0.108±0.031	0.418	0.097±0.032	0.873	0.112±0.03	0.823
	Glutamate (p)	0.115±0.036	0.817	0.107±0.044	0.114	0.115±0.03	0.913
	Succinate (p)	0.183±0.042	0.485	0.166±0.059	0.424	0.186±0.047	0.418
	LEAK (p)	0.03042±0.00825	**0.034**	0.02643±0.0104	0.093	0.02339±0.00745	0.6872
	ETSC (p)	0.177±0.054	0.453	0.162±0.056	0.111	0.188±0.06	0.462
	Rotenone (p)	0.073±0.026	0.941	0.075±0.025	0.723	0.076±0.031	0.338

Mean ± SD; p – significance level in reference to controls. PR – physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity measured after titration with uncoupler (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, FCCP), IR – initial respiration in washed

platelets before permeabilization with digitonin, DMP – respiration measured after the addition of digitonin+malate+pyruvate, ADP – stage 3 respiration supported through Complex I measured after the addition of ADP, Glutamate – stage 3 respiration measured after the addition of glutamate, Succinate – state 3 respiration supported through both Complex I and Complex II measured after the addition of the succinate, Rotenone – respiration after Complex I inhibition measured after the addition of rotenone. (p) indicate permeabilized platelets.

In intact platelets, the nonphosphorylating respiration measured after the addition of oligomycin (LEAK) was significantly higher in BPD patients with mania than in controls ($p=0.005$). LEAK was also higher in patients with depression than in controls, and higher in patients with mania than in patients with depression, though the difference did not reach statistical validity. Other indexes such as electron transport system capacity (ETSC) and respiration after inhibiting complex I with rotenone (Rotenone) were lower in patients in both phases of BPD than in healthy controls, and lower in depression than in mania, though these differences were not significant. Physiological respiration (PR) appeared to be similar in all the subgroups (Fig 7, 8, 9).

52. Castillo M., Kwock L. Et al. Proton MR spectroscopy in children with bipolar affective disorder: preliminary observations. AJNR Am J Neuroradiol 2000; 21: 832−838.
53. Cataldo A.M., McPhie D.L. et al. Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. Am J Pathol. 2010. Aug;177(2):575-85.
54. Cecil K.M., DelBello M.P. et al. Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. Bipolar Disord 2002; 4: 357−365.
55. Cerullo M.A., Adler C.M. et al. The functional neuroanatomy of bipolar disorder. Int. Rev. Psychiatry 2009; 21: 314–322.
56. Chang K., Adleman N. et al. Decreased N-acetylaspartate in children with familial bipolar disorder. Biol. Psychiatry, 53 (2003), pp. 1059-1065.
57. Chen G., Huang L.D. et al. The mood-stablizing agent valproate inhibits the activity of glycogen synthase kinase-3. J Neurochem 1999;72:1327-30.
58. Chen G., Zeng W.Z. et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J Neurochem. 1999 Feb; 72(2):879-82.
59. Chen S., Owens G.C., Edelman D.B. Dopamine inhibits mitochondrial motility in hippocampal neurons. PLoS One. 2008;3:e2804.
60. Chen S.L., Lee S.Y. et al. The BDNF Val66Met polymorphism and plasma brain-derived neurotrophic factor levels in Han Chinese patients with bipolar disorder and schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014; 51: 99–104.
61. Chepenik L.G., Fredericks C. et al. Effects of the brain-derived neurotrophic growth factor val66- met variation on hippocampus morphology in bipolar disorder. Neuropsychopharmacology 2009; 34: 944–951.

42. Bourgeron T., Rustin P. et al. Mutation of a nuclear succinate dehydrogenase gene results in mitochondrial respiratory chain deficiency. Nat Genet. 1995 Oct;11(2):144-9.
43. Brenner-Lavie H., Klein E., Ben-Shachar D. Mitochondrial complex I as a novel target for intraneuronal DA: modulation of respiration in intact cells. Biochem Pharmacol. 2009;78:85–95.
44. Bronfman F.C., Lazo O.M. et al. Spatiotemporal intracellular dynamics of neurotrophin and its receptors. Implications for neurotrophin signaling and neuronal function. Handb. Exp. Pharmacol. 2014; 220: 33–65.
45. Brown N.C., Andreazza A.C., Young L.T. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res. 2014 Aug 15;218(1-2):61-8.
46. Burkhardt C., Kelly J.P. et al. Neuroleptic medications inhibit complex I of the electron transport chain. Ann Neurol 1993;33:512-7.
47. Burnet B.B., Gardner A., Boles R.G. Mitochondrial inheritance in depression, dysmotility and migraine? J Affect Disord 2005; 88: 109— 116.
48. Byrne E., Dennett X. et al. Partial cytochrome oxidase (aa3) deficiency in chronic progressive external ophthalmoplegia. Histochemical and biochemical studies. J Neurol Sci. 1985 Dec;71(2-3):257-71.
49. Calvo S., Jain M. et al. Systematic identification of human mitochondrial disease genes through integrative genomics. Nat Genet. 2006 May;38(5):576-82.
50. Cannon D.M., Carson R.E. et al. Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. Arch. Gen. Psychiatry 2006; 63: 741–747.
51. Cannon D.M., Klaver J.K. et al. Genetic variation in cholinergic muscarinic-2 receptor gene modulates muscarinic2-receptor binding in vivo and accounts for reduced binding in bipolar disorder. Mol. Psychiatry 2011; 16: 407–418.

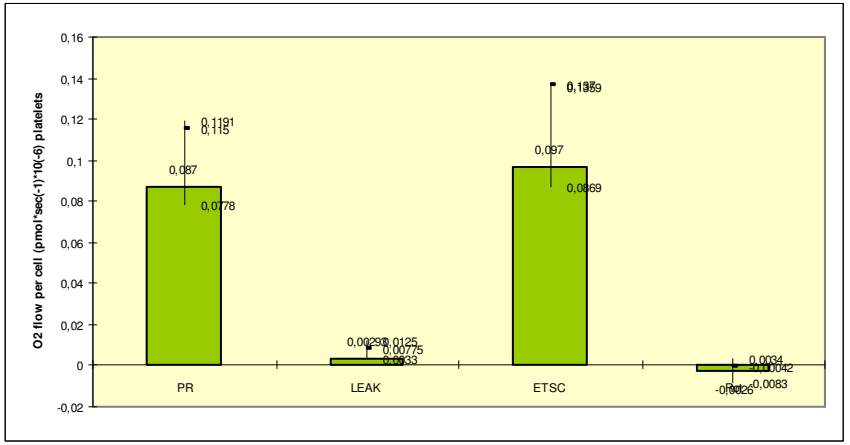

Fig. 7. Mitochondrial respiration normalized for platelet concentration in intact platelets of patients with BPD in depressive episode. PR - physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity, Rot – respiration after complex I inhibition, measured after the addition of rotenone.

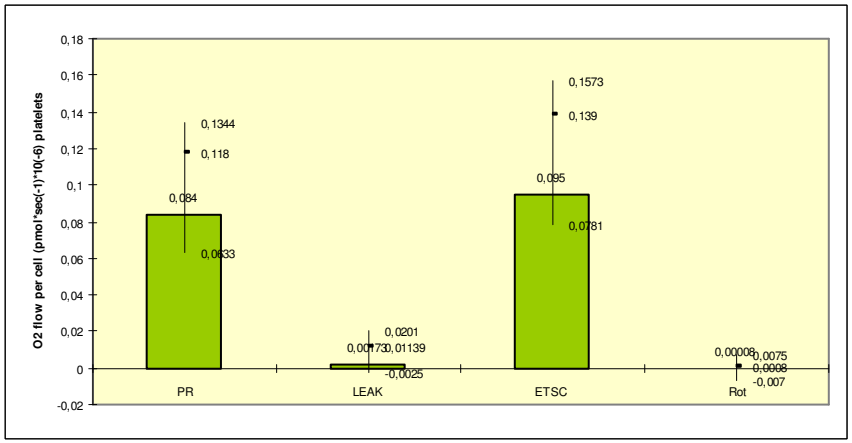

Fig. 8. Mitochondrial respiration normalized for platelet concentration in intact platelets of patients with BPD in manic episode. PR - physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of

oligomycin, ETSC – electron transport system capacity, Rot – respiration after complex I inhibition, measured after the addition of rotenone.

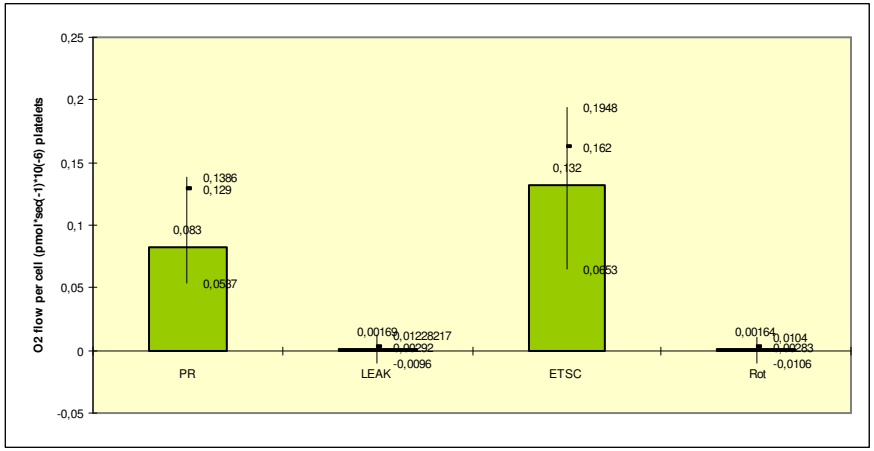

Fig. 9. Mitochondrial respiration normalized for platelet concentration in intact platelets of healthy controls. PR - physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity, Rot – respiration after complex I inhibition, measured after the addition of rotenone.

After the normalization for CS activity, mitochondrial respiratory rate did not show any significant difference between the group of patients with BPD in a manic episode and control group or between the group of patients with BPD in a manic or depressive episode.

We also measured a flux control ratio (the ratio of a respiratory rate at a specific respiratory state divided by ETSC); e.g. LEAK/ETSC ratio was significantly higher in patients with

32. Bielecka A.M., Obuchowicz E. Antiapoptotic action of lithium and valproate. Pharmacol Rep. 2008 Nov-Dec;60(6):771-82.
33. Björkholm C., Monteggia L.M. BDNF – a key transducer of antidepressant effects. Neuropharmacology 2016; 102: 72–79.
34. Blass J.P., Avigan J., Uhlendorf B.W. A defect in pyruvate decarboxylase in a child with an intermittent movement disorder. J Clin Invest. 1970 Mar;49(3):423-32.
35. Boado R.J., Pardridge W.M. Comparison of blood–brain barrier transport of glial-derived neurotrophic factor (GDNF) and an IgG-GDNF fusion protein in the rhesus monkey. Drug Metab. Dispos. 2009; 37: 2299–2304.
36. Boles R.G., Burnett B.B. et al. A high predisposition to depression and anxiety in mothers and other matrilineal relatives of children with presumed maternally inherited mitochondrial disorders. Am J Med Genet Neuropsychiatr Genet 2005; 137: 20—24.
37. Bora E., Fornito A. et al. Voxelwise metaanalysis of gray matter abnormalities in bipolar disorder. Biol. Psychiatry 2010; 67: 1097–1105.
38. Bora E., Pantelis C. Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. Schizophr. Bull., 41, 2015, pp. 1095-1104.
39. Bosetti F., Seemann R. Et al. Analysis of gene expression with cDNA microarrays in rat brain after 7 and 42 days of oral lithium administration. Brain Res Bull 2002;57:205-9.
40. Bossy-Wetzel E., Barsoum M.J. et al. Mitochondrial fission in apoptosis, neurodegeneration and aging. Curr Opin Cell Biol. 2003;15:706–716.
41. Boudreault F., Grygorczyk R. Cell swelling-induced ATP releaze is tightly dependent on intracellular calcium elevations. J.Physiol., 2004, 197, p. 205-213.

patients with mitochondrial cytopathies. J Cereb Blood Flow Metab 1993; 13: 469−474.
22. Barbosa I.G., Huguet R.B. et al. Impaired nerve growth factor homeostasis in patients with bipolar disorder. World J. Biol. Psychiatry 2011; 12: 228–232.
23. Benes F.M., Matzilevich D. et al. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry. 2006 Mar;11(3):241-51.
24. Ben-Shachar D., Karry R. Neuroanatomical pattern of mitochondrial complex I pathology varies between schizophrenia, bipolar disorder and major depression. PLoS One. 2008;3 (11):e3676.
25. Ben-Shachar D., Zuk R. et al. Increased mitochondrial Complex I activity in platelets of schizophrenic patients. Int J Neuropsychopharmacol. 1999. Dec 2(4): 245-53.
26. Berk M., Berk L. et al. Stage managing bipolar disorder. Bipolar Disord. 2014; 16: 471–477.
27. Berk M., Dodd S. et al. Dopamine dysregulation syndrome: Implications for a dopamine hypothesis of bipolar disorder. Acta Psychiatr. Scand. Suppl. 2007; 434: 41–49.
28. Berk M., Kapczinski F. et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 2011; 35: 804–817.
29. Berk M., Kapczinski F. et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev., 2011. 35, pp. 804-817
30. Bertolino A., Frye M. et al. Neuronal pathology in the hippocampal area of patients with bipolar disorder: a study with proton magnetic resonance spectroscopic imaging. Biol Psychiatry 2003; 53: 906−913.
31. Bezchlibnyk Y.B., Wang J.F. et al. Gene expression differences in bipolar disorder revealed by cDNA array analysis of post-mortem frontal cortex. J Neurochem. 2001 Nov;79(4):826-34.

BPD in a manic episode than in healthy controls (p=0.03) and in patients with BPD in a depressive episode than in healthy controls (p=0.042) (Fig. 10, 11)

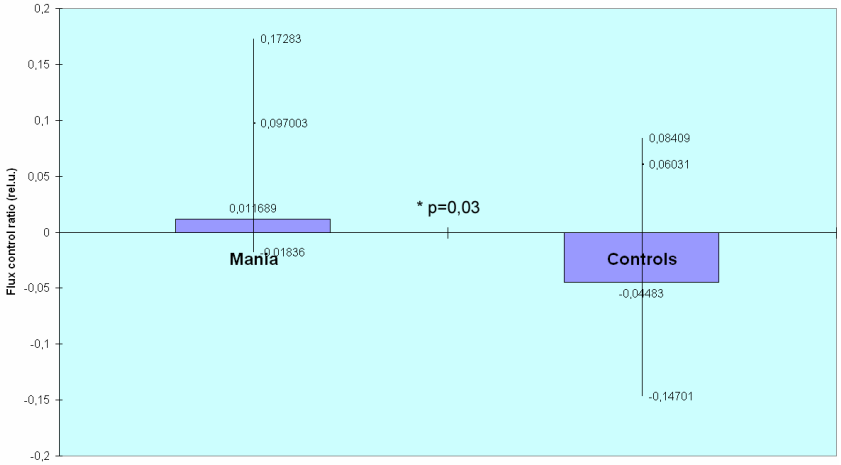

Fig. 10. The LEAK/ETSC index (flux control ratio) in intact platelets of patients with mania and healthy controls, p=0.03

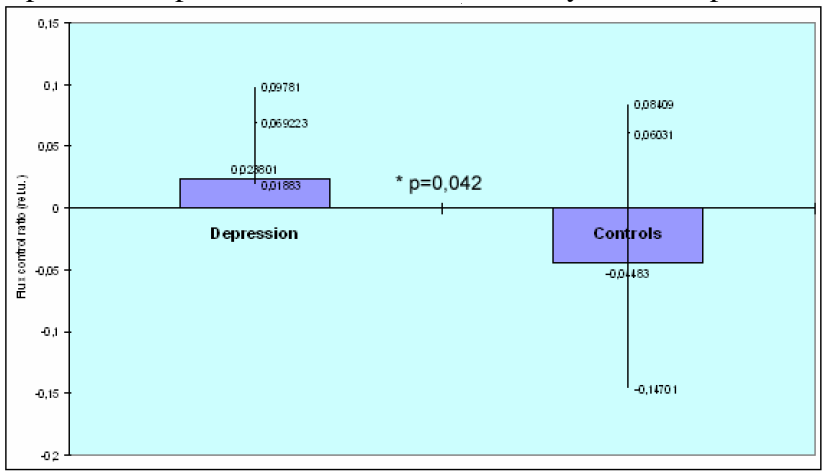

Fig. 11. The LEAK/ETSC index (flux control ratio) in intact platelets of patients with depression and healthy controls, p=0.042

The mean LEAK/ETSC in intact platelets of patients with BPD episode was slightly higher in BPD patients in both manic and depressive episodes compared to controls, which may indicate a disturbance in the mitochondria coupling process and/or functional integrity in the inner mitochondrial membrane in BPD.

In permeabilized platelets LEAK index (nonphoshorylating respiration after the addition of oligomycin) was also significantly higher in BPD patients with mania ($p=0.034$) than in healthy controls. LEAK was also lower in patients with depression than in patients with mania, though these changes did not reach statistical validity ($p=0.058$). Other respiratory rates such as ADP, Succinate did not reveal a significant difference between the groups.

The results are summarized in Table 5 and Fig. 12.

12. Andreazza A.C., Shao L. et al. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the pre-frontal cortex of patients with bipolar disorder. Arch Gen Psychiatry. 2010;67:360–8.
13. Andreazza A.C., Wang J.F. et al. Specific subcellular changes in oxidative stress in prefrontal cortex from patients with bipolar disorder. J Neurochem. 2013 Nov;127(4):552-61.
14. Andreazza A.C., Young L.T. The neurobiology of bipolar disorder: Identifying targets for specific agents and synergies for combination treatment. Int. J. Neuropsychopharmacol. 2014; 17: 1039–1052.
15. Anglin R.E., Garside S.L. et al. The psychiatric manifestations of mitochondrial disorders: a case and review of the literature. J Clin Psychiatry. 2012 Apr;73(4):506-12.
16. Aronis A., Melendez J.A. et al. Potentiation of Fasmediated apoptosis by attenuated production of mitochondria-derived reactive oxygen species. Cell Death Differ 2003;10(3): 335-344.
17. Aydemir O., Cubukcuoglu Z. et al. Oxidative stress markers, cognitive functions, and psychosocial functioning in bipolar disorder: an empirical cross-sectional study. Rev. Bras. Psiquiatr., 36. 2014, pp. 293-297.
18. Bachmann R.F., Wang Y. et al. Common effects of lithium and valproate on mitochondrial functions: protection against methamphetamine-induced mitochondrial damage. Int J Neuropsychopharmacol. 2009 Jul; 12(6): 805–822.
19. Banerjee U., Dasgupta A. Et al. Effects of lithium therapy on Na+-K+-ATPase activity and lipid peroxidation in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012;37:56–61.
20. Barbiroli B., Montagna P. et al. Abnormal brain and muscle energy metabolism shown by ^{31}P magnetic resonance spectroscopy in patients affected by migraine with aura. Neurology 1992; 42: 1209−1214.
21. Barbiroli B., Montagna P. et al. Defective brain energy metabolism shown by in vivo ^{31}P MR spectroscopy in 28

7. Použitá literatura

1. aan het Rot M., Mathew S.J., Charney D.S. Neurobiological mechanisms in major depressive disorder. CMAJ: Can. Med. Assoc. J. 2009; 180: 305–313.
2. Abdel-Razaq W., Kendall D.A., Bates T.E. The effects of antidepressants on mitochondrial function in a model cell system and isolated mitochondria. Neurochem Res. 2011;36:327-38.
3. Abramov A.Y., Smulders-Srinivasan T.K. et al. Mechanism of neurodegeneration of neurons with mitochondrial DNA mutations. Brain. 2010. 133, 797–807.
4. Abu-Amero K.K., Bosley T.M. Mitochondrial abnormalities in patients with LHON-like optic neuropathies. Invest. Ophthalmol. Vis. Sci. 2006. 47, 4211–4220.
5. Afanas'ev I. Signaling and damaging functions of free radicals in aging-free radical theory, hormesis, and TOR. Aging And Disease. 2010;1(2) 75-88.
6. Alexeyev M.F., LeDoux S.P., Wilson G.L. Mitochondrial DNA and aging. Clinical Science. 2004. 107, 355–364.
7. Allison J.H., Stewart M.A. Reduced brain inositol in lithium-treated rats. Nat New Biol 1971; 233: 267−268.
8. Anand A., Barkay G. et al. Striatal dopamine transporter availability in unmedicated bipolar disorder. Bipolar Disord. 2011; 13: 406–413.
9. Anderson S., Bankier A.T. et al. Sequence and organization of the human mitochondrial genome. Nature 1981; 290: 457–65.
10. Anderson G., Maes M. Bipolar disorder: Role of immuneinflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. Curr. Psychiatry Rep. 2015; 17: 8.
11. Andreazza A.C., Frey B.N. et al. DNA damage in bipolar disorder. Psychiatry Res. 2007 Sep 30; 153(1):27-32.

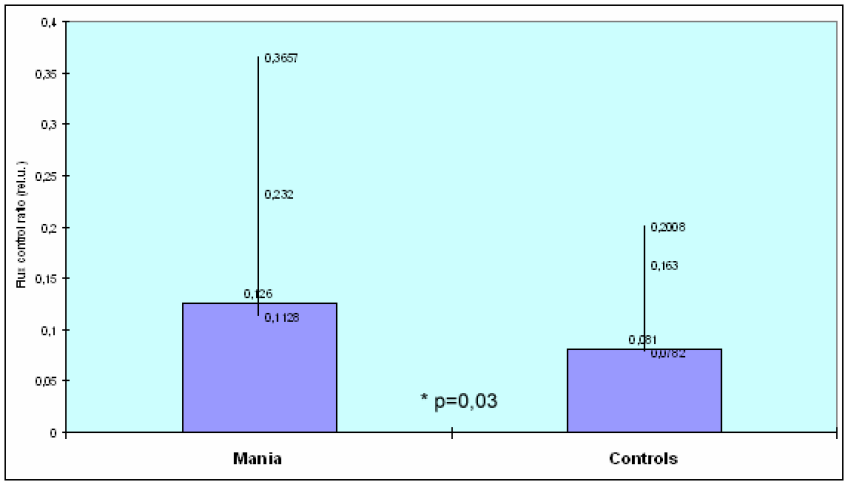

Fig. 12. The LEAK/ETSC index (a part of the flux control ratio) in permeabilized platelets of patients with BPD with mania and healthy controls, p=0.042

A comparable analysis for the mitochondrial enzymes activity and mitochondrial respiration in the group of BPD patients in remission and healthy controls was also performed. The comparability of the indexes in subgroups A and B was estimated through Student t-test. The results are summarized in Tab. 6.

Tab. 6. Mitochondrial respiration in the blood platelets from patients with bipolar disorder (measurement 2, remission) and healthy controls

	Mitochon-drial function	Groups					
		Mania	P (Mania vs Controls)	Depression	P (Depression vs Controls)	Controls	P (Mania vs Depression)
Intact platelets	PR	0.106± 0.029	0.982	0.106± 0.024	0.362	0.106± 0.023	0.533
	LEAK	0.00466± 0.00088	**0.049**	0.00356± 0.00101	0.573	0.00169± 0.00123	0.174
	ETSC	0.127± 0.039	0.64	0.129± 0.031	0.677	0.132± 0.03	0.462
	Rotenone	-0.0007± 0.00045	0.079	0.00075± 0.0006	0.185	0.00164± 0.00119	0.788
Permeabilized platelets	IR (p)	0.084± 0.028	0.158	0.089± 0.025	0.663	0.094± 0.021	0.211
	DMP (p)	0.037± 0.013	0.856	0.037± 0.013	0.56	0.038± 0.014	0.33
	ADP (p)	0.107± 0.042	0.649	0.0109± 0.035	0.267	0.112± 0.03	0.583
	Glutamate (p)	0.118± 0.049	0.788	0.116± 0.041	0.145	0.115± 0.03	0.672
	Succinate (p)	0.188± 0.065	0.913	0.187± 0.053	0.989	0.186± 0.047	0.699
	LEAK (p)	0.0283± 0.01152	0.068	0.0256± 0.00984	0.164	0.02339± 0.00745	0.13
	ETSC (p)	0.185± 0.071	0.892	0.186± 0.065	0.463	0.188± 0.06	0.462
	Rotenone (p)	0.081± 0.033	0.601	0.079± 0.032	0.555	0.076± 0.031	0.54

Mean ± SD; p – significance level in reference to controls . PR – physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity measured after titration with uncoupler (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, FCCP), IR – initial respiration in washed platelets before permeabilization with digitonin, DMP –respiration measured after the addition of digitonin+malate+pyruvate, ADP – stage 3

the LEAK index was significantly higher in BPD patients with remission than in healthy controls.

Additional results of the study include the exploration of the duration period between the acute state and remission and its dependence on the mitochondrial pathology indicators in patients with different phases of BPD. Indicators sensitive for the period length turned out to be: CS (positive values), COX (negative values), PR (positive values), ETS capacity (negative values), and respiration after the addition of glutamate (positive values).

Taken together, the obtained data provide evidence for the connection between psychopathological symptoms and mitochondrial function in mental disorders through cellular mechanisms involved in the pathology of BPD explored in the current study.

Results from this study provide information for clinicians and other researchers. This study also portrays mitochondria as a promising targets for the therapeutic modulation of cellular resilience and synapses in neuronal pathways involved in high-order functions of the brain in different mental disorders, including BPD.

Further research focused on treatment of this disorder, therapeutic strategies and diagnostic tools is needed to acquire a better understanding of BPD pathophysiology.

Healthy controls do not show this type of mitochondrial alteration. Obtaining peripheral blood platelets from patients with mental disorders is an easy and quick procedure which may be useful for *in vivo* studies of mitochondrial respiration in psychiatric diseases;

- support Hypothesis 2 that the severity of the symptoms of BPD is associated with the severity of the alteration of the mitochondrial function. A significant correlation was observed between Complex I and BPRS score in patients with manic symptoms;

- do not support Hypothesis 3 that there is a difference in the levels of mitochondrial respiration and enzyme activity in manic state and depressive state. There was no significant difference in mitochondrial respiration and enzymes activity between subgroups of BPD patients in mania and depression.

- support Hypothesis 4 that there is a difference in the levels of mitochondrial respiration and enzyme activity in patients with BPD and healthy controls both in acute state and remission. LEAK index both in intact and permeabilized platelets was significantly higher in BPD patients with mania than in controls; flux control ratio (the ratio of a respiratory rate at a specific respiratory state divided to ETSC) was significantly higher in patients with mania than in controls and in patients with depression than in controls; in intact platelets,

respiration supported through Complex I measured after the addition of ADP, Glutamate – stage 3 respiration measured after the addition of glutamate, Succinate – state 3 respiration supported through both Complex I and Complex II measured after the addition of the succinate, , Rotenone – respiration after Complex I inhibition measured after the addition of rotenone. (p) indicate permeabilized platelets.

In intact platelets, the LEAK was significantly higher in patients with bipolar disorder in remission after a manic episode (0.00466 $pmol \cdot sec^{-1} \cdot 10^{-6}$ platelets) than in controls (0.00169 $pmol \cdot sec^{-1} \cdot 10^{-6}$ platelets, $p<0.05$) (Fig. 13). Other indexes such as ETSC and respiration after inhibiting complex I with rotenone (Rotenone) were lower in patients with patients with bipolar disorder in remission after a manic episode than in healthy controls, however these differences were not significant. PR index was similar in both groups. After the normalization for CS activity, the mitochondrial respiratory rate had shown no significant difference between the group of patients with bipolar disorder in remission after a manic episode or a depressive episode and control group.

In permeabilized platelets there was no significant difference in the mitochondrial respiration for all the respiratory states.

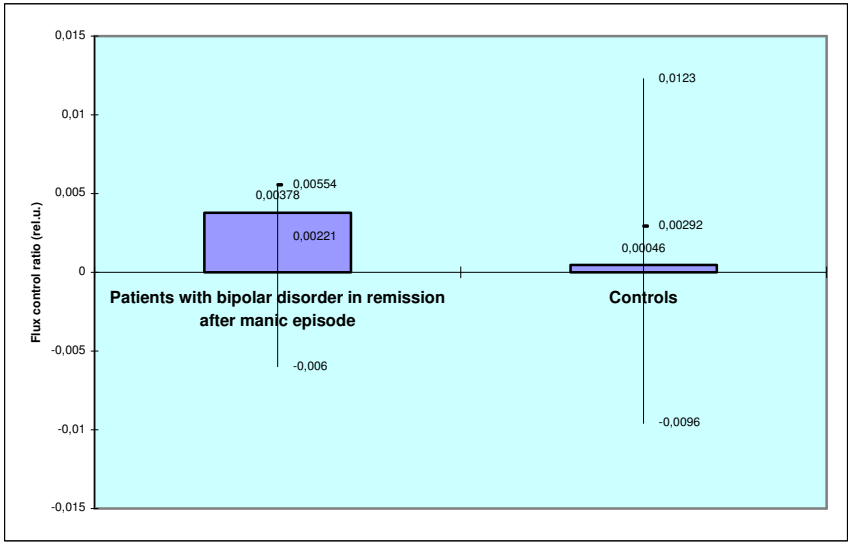

Fig. 13. The LEAK index in intact platelets of patients with bipolar disorder in remission after manic episode and healthy controls, p=0,042

4.3. Changes in mitochondrial function of BPD patients during the research period

An assessment of the changes in mitochondrial enzymes activity and mitochondrial respiration of BPD patients during the research period was also performed, i.e. values in the acute phase before treatment (manic or depressive episode) and after treatment (in remission) were compared (Tab. 7).

6. Závěry

BPD is a complex disease that involves several biological pathways. Mitochondrial dysfunction was included when the mitochondrial hypothesis of BPD was firstly proposed by Kato in 2000. Since then it was supported by various data including decreased ATP production, upregulation of genes involved in apoptosis, downregulation of mitochondrial genes regulating OXPHOS, decreased antioxidant defences, abnormalities in the structure, and distribution of mitochondria and others. Some of the pathophysiological processes in BPD were discovered to be associated with certain clinical symptoms of the disease such as cognitive impairment, hyperactivity and others.

The main research question in the conducted study was whether energy metabolism in mitochondria corresponds to clinical evaluation of the psychopathological symptoms in patients with bipolar disorder.

The results obtained by the current study:

- support Hypothesis 1 that there is a set of mitochondrial functional impairment indexes specific for the current phase of the disorder. For patients with BPD we can expect a decrease in ETSC and physiological respiration in intact platelets, and an increase in DMP, nonphosphorylation respiration and initial respiration in permeabilized platelets.

respiration rates easily obtained from peripheral blood platelets might become a useful clinical tool in the diagnostic process.

A unique combination of the factors above in further studies may help to understand the effect of the certain mitochondrial function alteration on specific behaviors and psychopathological symptoms. Regardless of the rank of the certain index in the sequence of disease-causing events, an overall mitochondrial pathology is an important factor in the manifestation of clinical symptoms of BPD.

Tab. 7. Activities of mitochondrial enzymes in platelets of BPD patients in acute phase of the disease compared with remission

Mitochondrial enzymes	Phase of the disease	Disease state		p
		Acute	Remission	
CS, nmol·min^{-1}·mg^{-1}	Mania	68.9±11.8	63.9±9.7	0.063
	Depression	64.0±19.6	65.3±19.3	0.687
CI, nmol·min^{-1}·mg^{-1}	Mania	53.2±19.0	59.3±27.8	0.526
	Depression	57.8±22.9	80.2±19.3	0.352
CII, nmol·min^{-1}·mg^{-1}	Mania	8.07±3.96	7.62±3.33	0.467
	Depression	7.87±3.41	8.09±3.41	0.799
COX, nmol·min^{-1}·mg^{-1}	Mania	19.44±5.91	19.39±4.29	0.985
	Depression	15.03±5.57	15.57±5.43	0.72

Mean ± SD; p – significance level. CS – citrate synthase, CI – Complex I, CII – Complex II, COX – Complex IV.

The CS activity in BPD patients with mania was higher than in healthy controls though the difference did not reach statistical validity (p=0,063). The difference between other enzymes activity such as CI, CII and COX for the groups of BPD patients and healthy controls also did not reach statistical validity. The results are summarized in Fig. 14.

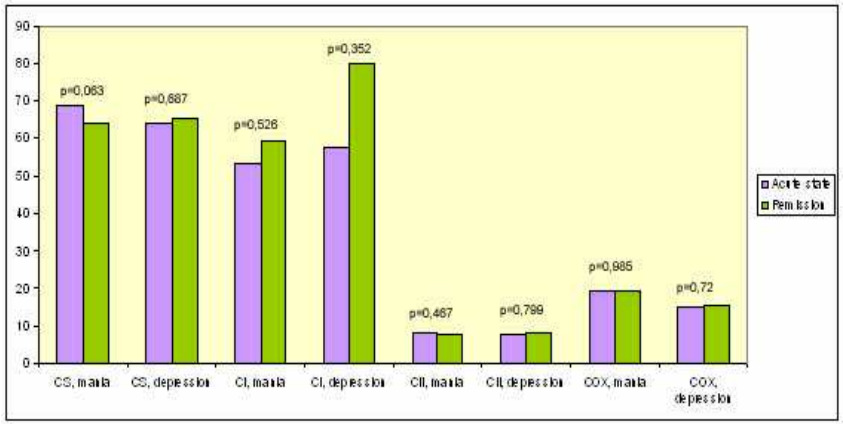

Fig. 14. Activities of mitochondrial enzymes in patients with BPD in an acute phase of the disease (manic or depressive episode) compared with remission

We have also compared the mitochondrial enzymes activity and respiration rates in the subgroups A and B: patients with mania vs patients with depression. The results obtained through paired test calculation are summarized in Tab. 9.

Tab. 9. Mitochondrial respiration in blood platelets from patients with bipolar disorder in manic or depressive episodes before and after treatment

	Respiratory state	Episode of the disease	Disease state		p
			Acute	Remission	
Intact platelets	PR	Mania	0.105±0.017	0.106±0.033	0.885
		Depression	0.101±0.014	0.106±0.022	0.538
	LEAK	Mania	0.00656±0.00483	0.00548±0.00121	0.431
		Depression	0.00534±0.00241	0.00301±0.00095	0.079
	ETSC	Mania	0.124±0.022	0.129±0.044	0.604
		Depression	0.117±0.02	0.123±0.025	0.559

needs to be present in certain brain areas involved in certain clinical symptoms of the disease. Bioenergetic demand of the brain cells may vary in different brain areas and this demand is sensitive to different factors, which means that there is a certain threshold value of damaged mitochondria causing a symptom available for clinical measurement, and this value may be different for different neurons. These differences might enable some psychopathological symptoms to manifest while other symptoms remain hidden.

Explored abnormalities in mitochondrial function may reduce the cell ability for the appropriate stress response to such stimuli as emotional outbursts (an increased glutamate release), starvation (decreased glucose levels) and other risk factors known for psychotic episodes in affective disorders such as in-utero and infant malnutrition, substance abuse, and traumatic experiences (Kroll JL, 2007).

If we suggest that the obtained abnormalities in platelet mitochondrial respiration are similar to the abnormalities in brain mitochondrial respiration, it may further confirm the contribution of energy metabolism impairment to the pathophysiology of BPD. Given the lack of a reliable and clinically relevant biological markers for BPD and other mood disorders, a set of mitochondrial enzymes activity and

NAA/Creatine + Phosphocreatine or NAA levels and illness duration. However, later studies found that decreased NAA levels was restricted to the basal ganglia of the brain (Chang K et al, 2003). Berk proposed a general role of mitochondrial dysfunction in the disease progression (Berk M et al, 2011). Discemibly there is no suggested clinical test for a combination of the mitochondrial impairment indicators for the BPD, and therefore the data obtained from the current research may serve as an easily-accessible set of predictors for the episode duration in clinical practice.

There are few research findings confirming the role of mitochondrial respiration in the severity of the clinical symptoms of BPD (Scaini G et al, 2016). A body of evidence for the increased mitochondrial respiration and ATP production in a manic phase and decreased mitochondrial function in patients in the euthymic or depressive phase of the BPD was found, though the research data are partially controversial (Hroudova J, Fisar Z, 2011). It has yet to be discovered whether the impairment in mitochondrial function contributes to the disease process or is an independent process.

Various mitochondrial function alterations in patients with BPD do not indicate the same behavioral changes or psychopathological symptoms regardless of the tissue type or brain area. We suggest that the same mitochondrial impairment

	Rotenone	Mania	0.00044± 0.00036	-0.00044± 0.00026	0.207
		Depression	-0.00151± 0.00109	-0.00121± 0.00074	0.989
Permeabilized platelets, pmol*sec^{-1}*10^{-6}	IR (p)	Mania	0.087±0.021	0.083±0.028	0.349
		Depression	0.082±0.026	0.088±0.029	0.629
	DMP (p)	Mania	0.046±0.028	0.038±0.014	0.215
		Depression	0.034±0.014	0.036±0.012	0.555
	ADP (p)	Mania	0.108±0.031	0.107±0.049	0.964
		Depression	0.097±0.032	0.108±0.029	0.547
	Glutamate (p)	Mania	0.115±0.036	0.114±0.055	0.925
		Depression	0.107±0.044	0.125±0.039	0.478
	Succinate (p)	Mania	0.183±0.042	0.186±0.072	0.945
		Depression	0.166±0.059	0.192±0.055	0.429
	LEAK (p)	Mania	0.03042± 0.00825	0.02939± 0.01298	0.552
		Depression	0.02643±0.0104	0.02647± 0.00858	0.66
	ETSC (p)	Mania	0.177±0.054	0.183±0.082	0.775
		Depression	0.162±0.056	0.186±0.049	0.49
	Rotenone (p)	Mania	0.073±0.026	0.077±0.031	0.799
		Depression	0.075±0.025	0.089±0.039	0.448

Mean ± SD; significance level. PR – physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity measured after titration with uncoupler (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, FCCP), IR – initial respiration in washed platelets before permeabilization with digitonin, DMP –respiration measured after the addition of digitonin+malate+pyruvate, ADP – stage 3 respiration supported through Complex I measured after the addition of ADP, Glutamate – stage 3 respiration measured after the addition of glutamate, Succinate – state 3 respiration supported through both Complex I and Complex II measured after the addition of the succinate, Rotenone – respiration after Complex I inhibition measured after the addition of rotenone. (p) indicate permeabilized platelets.

There were no significant differences between an acute stage of illness and remission in BPD patients ($p>0.05$ for all the measurements).

4.4. Connections between mitochondrial function and psychopathological symptoms in BPD patients

We also calculated correlation coefficients between the BPRS, YMRS, MADRS, MDQ and CGI-I tests and mitochondrial complexes activity to establish the association between the state of the disease, psychopathological symptoms, clinical improvement and mitochondrial pathology. A significant correlation was observed between Complex I and the BPRS score in the subgroup A (patients with mania, acute state – measurement 1) ($p=0.001$). The Pearson coefficient showed a high closeness of relationships according to Chaddock scale ($r_{xy} = 0.747$), which is the evidence of the correlation validity. The paired linear regression equation shows the Complex I value dependence of BPRS score (1):

$$BPRS = 18.66 + 0.7*CI \quad (1)$$

where BPRS – Brief Psychiatric Rating Scale, mental state assessment scale in patients with BPD, manic episode, acute state (points), CI – Complex I activity ($nmol \cdot min^{-1} \cdot mg^{-1}$).

Based on the regression coefficient value, with the CI increase of 1 $nmol \cdot min^{-1} \cdot mg^{-1}$ we expect a BPRS score increase of 0.7 points. The coefficient of determination R^2 was 0.558 which indicates that 55.8% factors are taken into account in the regression model (1).

control ratio increase in patients with BPD seems to be mania-specific, though we did not obtain any data confirming a decrease of the same indexes during the depressive phase.

Factor analysis in our study showed that patients with BPD had significantly lower Factor 2 values than healthy controls (ETS capacity and physiological respiration in intact platelets) and significantly higher Factor 3 values than healthy controls (stage 3 respiration, nonphosphorylation respiration and initial respiration in permeabilized platelets).

We speculate that a combination of those indexes with LEAK index and flux control ratio may serve as a clinical set of biological markers specific for the diagnosis of the bipolar disorder regardless of the phase of the disease.

The current study also explores the duration period between the acute state and remission and its dependence on the mitochondrial pathology indicators in blood platelets of the patients with different phases of BPD. Indicators sensitive for the period length turned out to be: CS (positive values), COX (negative values), PR (positive values), ETS capacity (negative values), and respiration after the addition of glutamate (positive values).

A possible connection between the illness duration and mitochondrial dysfunction in patients with BPD was also studied by Chang, who found a negative correlation between

to controls, though normalization for CS activity eliminated the difference. The LEAK respirations, as well as the flux control ratio LEAK/ETSC, are parameters characterizing mitochondrial damage. The flux control ratio LEAK/ETSC (i.e., oligomycin-inhibited respiration divided by uncoupled respiration at optimum FCCP concentration) in intact platelets remained very low, which indicated well-coupled mitochondria and the functional integrity of the inner mitochondrial membrane.

Flux control ratio for the intact platelets (the ratio of a respiratory rate at a specific respiratory state divided to ETS capacity) was also significantly higher both in patients with BPD in a manic state and in a depressive state than in healthy controls. This may indicate an increased intrinsic uncoupling in the platelets of BPD patients and the availability of these parameters as indicators of the platelet respiration.

Morris et al. (2017) postulates that symptomatically BPD is a biphasic disorder of energy ability; increased in mania and decreased in depression; and mitochondrial dysfunction may serve as a state dependent marker of the disorder with an increased mitochondrial function during mania and a decreased mitochondrial function during depression. The author offers a model explaining the biphasic nature of the disorder (Morris G et al, 2017). Our data partially corresponds with this postulate as the obtained data for the LEAK index increase and flux

The regression function diagram (1) is shown on the Fig. 15.

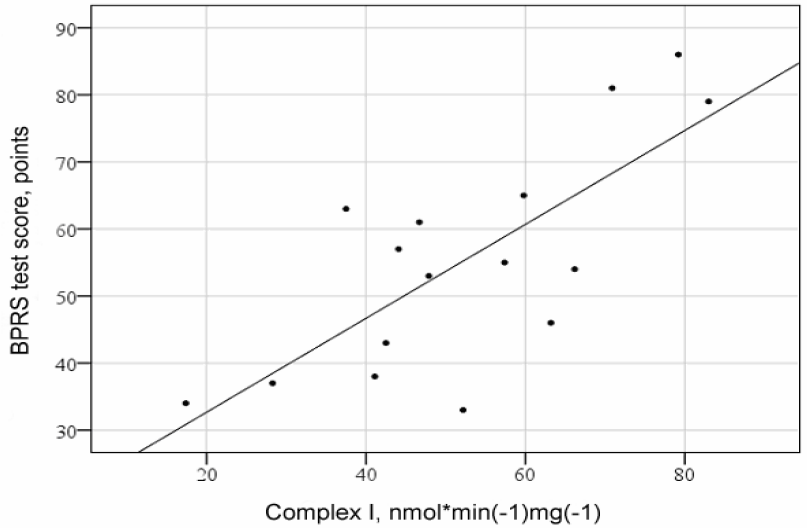

Fig. 15. Linear dependence diagram for the mental state of BPD patients with mania and Complex I activity

There were no significant correlation coefficients between other mental state assessment tests and mitochondrial pathology indicators in the other subgroups of the patients and in healthy controls.

In order to identify relationships between a large numbers of mitochondrial pathology indicators in the research, a factor analysis was performed. We could distinguish four factors through principal component analysis with a Varimax rotation method. The characteristics of these factors are summarized in Tab. 9.

Tab. 9. The characteristics of the mitochondrial pathology assessment factors in patients with bipolar disorder

Factor No.	Meaning	Total variance explained, %	Cumulative % of the explained variance
1	3.62	30.17	30.17
2	2.66	22.19	52.36
3	2.27	18.87	71.23
4	1.28	10.67	81.9

The eigenvalues of all the factors were >1. The factor load for each of the mitochondrial pathology indicators allowing the evaluation of the correlation between picked factors and other indicators is shown as a factor loadings matrix where the highest values are shown in bold (Tab. 10).

Tab. 10. Factor loadings matrix

Mitochondrial function	Factor 1	Factor 2	Factor 3	Factor 4
Rotenone (p)	**.876**	.015	-.063	.299
Succinate (p)	**.860**	.352	.288	.039
ETSC (p)	**.821**	.400	.237	.091
ADP (p)	**.647**	.507	.473	-.108
Glutamate (p)	**.635**	.380	.509	-.110
ETSC	.165	**.938**	.090	.068
PR	.228	**.866**	.175	.190
DMP (p)	.085	.175	**.863**	.141
LEAK (p)	.568	-.054	**.602**	.207
IR (p)	.389	.485	**.586**	.042
Rotenone	.238	.277	-.104	**.730**
LEAK	-.011	-.043	.373	**.721**

mitochondrial respiration in both diseases. Those alterations in energy metabolism may partially define or underlay psychopathology in a manic state or during the psychotic episode of the disease. Alterations may also vary according to the state of the disease, with the positive peak in manic states, which can be measured and proved statistically and negative peak in depressive states which is downplayed. Further studies are needed to verify this suggestion.

Since Complexes I-IV play a key role in mitochondrial OXPHOS, their altered activity may reflect a mitochondrial dysfunction which, in turn, can result in impaired neuronal metabolism and neuronal plasticity expressed in certain psychopathological symptoms. Still there is not enough evidence whether this alteration is a causal or consequential effect of the disease.

We found that there was no statistical difference in physiological respiration in all the subgroups (BPD patients with mania, BPD patients with depression, BPD patients in remission, healthy controls). Therefore PR index cannot be used as biological marker sensitive to BPD.

In the respiration rates there was a significant increase of LEAK index (nonphosphorylating respiration measured after the addition of oligomycin) both in intact and permeabilized platelets in the subgroup of BPD patients with mania compared

participants and further research in this area will provide us with the necessary data.

Research covering the association of mitochondrial enzymes activity and psychopathological symptoms of the BPD are limited while research exploring those connections in patients with other psychiatric diseases are widely present. Ben-Shakhar repeatedly obtained results indicating the connection between the severity of the SZ symptoms and mitochondrial impairment (Ben-Shachar D et al, 1999, Ben-Shachar D et al, 2008) though there were no significant changes in the activity of complexes I and IV in mitochondria isolated from blood platelets of BPD patients in the same study. Dror et al. (2002) also performed a study exploring Complex I activity in schizophrenic and BPD patients and found that a degree of increase in complex I activity correlated directly with the severity of positive symptoms in patients with SZ (a tendency towards a negative correlation between complex I activity and negative symptoms did not reach statistical significance) (Dror N et al, 2002).

As many psychopathological symptoms and mitochondrial pathology found in patients with SZ and BPD overlap (Clay H et al, 2011), those findings may highlight a connection between the severity of psychopathological symptoms and a specific and selective alteration in

PR – physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity measured after titration with uncoupler (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, FCCP), IR – initial respiration in washed platelets before permeabilization with digitonin, DMP –respiration measured after the addition of digitonin+malate+pyruvate, ADP – stage 3 respiration supported through Complex I measured after the addition of ADP, Glutamate – stage 3 respiration measured after the addition of glutamate, Succinate – state 3 respiration supported through both Complex I and Complex II measured after the addition of the succinate, Rotenone – respiration after Complex I inhibition measured after the addition of rotenone. (p) indicate permeabilized platelets.

According to the components distribution, Factor 1 is characterized by high values of: respiration after Complex I inhibition, stage 3 respiration supported through both Complex I and II, electron transport system capacity and stage 3 respiration supported through Complex I, all in permeabilized platelets. Factor 2 is characterized by high values of: electron transport system capacity and physiological respiration in intact platelets. Factor 3 is characterized by high values of: initial respiration, respiration after addition of malate and pyruvate, and nonphosphorylating respiration, all in permeabilized platelets. Factor 4 is characterized by high values of: respiration after Complex I inhibition and nonphosphorylating respiration in intact platelets.

We made the assessment of the differences between the experimental and control group based on the calculated values for each of the identified factors. The values of the four

combined factors in the BPD patients and control groups were compared for that purpose (Tab. 11).

Tab. 11. The comparison of combined factors in patients with bipolar disorders and control group

Combined factors	Groups				p
	Bipolar disorder		Controls		
	Me	Q_1; Q_3	Me	Q_1; Q_3	
Factor 1 (Rotenone (p), Succinate (p), ETSC (p), ADP (p), Glutamate (p))	-0.2	-0.95; 0.81	0.19	-0.56; 0.52	0.543
Factor 2 (ETSC, PR)	-0.13	-0.89; 0.28	0.34	-0.34; 1.19	**0.024**
Factor 3 (DMP (p), Oligomycin (p), IR (p))	0.16	-0.59; 0.63	-0.32	-0.83; -0.06	**0.023**
Factor 4 (Rotenone, LEAK)	0.15	-0.6; 1.05	-0.15	-0.7; 0.64	0.325

Me – Mean; SD – Standard deviation; ; Q_1 – Quartile 1; Q_3 – Quartile 3; p – significance level. PR – physiological respiration, LEAK – nonphosphorylating respiration measured after the addition of oligomycin, ETSC – electron transport system capacity measured after titration with uncoupler (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, FCCP), IR – initial respiration in washed platelets before permeabilization with digitonin, DMP –respiration measured after the addition of digitonin+malate+pyruvate, ADP – stage 3 respiration supported through Complex I measured after the addition of ADP, Glutamate – stage 3 respiration measured after the addition of glutamate, Succinate – state 3 respiration supported through both Complex I and Complex II measured after the addition of the succinate, Rotenone – respiration after Complex I inhibition measured after the addition of rotenone. (p) indicate permeabilized platelets

with BPD (Aydemir O et al, 2014) and they are often present in the very first episode (Bora E, Pantelis C, 2015).

Continuing the discussion of the changes in mitochondrial respiration in depressive phase of the disease we need to mention Gardner, who performed a research on mitochondrial enzymes activity and ATP production rate in patients with MDD and found an overall decrease in Complex I-IV in comparison with controls which correlated with the vulnerability to psychopathology in the following scales: 'Somatic Anxiety'. 'Psychasthenia' and 'Suspition' (Gardner A et al, 2003).

Correa found a decreased level of ETS complexes in an animal model of mania associated with manic symptoms (Correa et al, 2007). Freitas discovered an association between manic-like hyperactivity in a rat brain and a decrease in the activity of CS (Freitas TP et al, 2010).

As seen from the results of the conducted analyses, in our research we didn't find any significant correlation between certain psychometric scales and mitochondrial respiration indexes except for the correlation between Complex I and BPRS score in patients with mania. Based on the regression coefficient value, with the CI increase of 1 $nmol*min^{-1}mg^{-1}$ we expect a BPRS score increase of 0,7 points. A low quantity of obtained correlations may be the result of the small amount of

complexes of mononuclear blood cells were examined in BPD patients in euthymic mood (Gubert C et al, 2013). No significant changes were found in complex I, complex II and complex II + III activities. The obtained results are also consistent with the data received by deSouza in 2014 which stated that mitochondrial complexes I-IV activity was not changed during the depressive episodes of BPD (deSouza RT et al, 2015).

A decrease in COX activity was observed in BPD patients with depression and when compared with BPD patients with mania, the significance level was close to critical (Fig. 6). This data partially corresponds with the previous research made by Valla (Valla J et al, 2006) on the groups of patients with mild cognitive deficits (Alzheimer disease and other diseases), and data discovered by Fisar (Fisar Z et al, 2016) for the group of patients with Alzheimer's disease, where COX activity was decreased and negatively correlated with the Mini Mental State Examination (MMSE) score. This may lead to a suggestion that a decreased complex IV activity indicates cognitive impairment which is more evident during a depressive phase of the disease. Prince found a decrease in COX activity in the frontal cortex and caudate nucleus and linked it to an increased emotional and cognitive impairment in patients with SZ. In general (Prince JA et al, 2000), neurocognitive deficits are commonly associated

The Mann-Whitney test shows that patients with bipolar disorder had significantly lower Factor 2 values than healthy controls (p=0.024) and significantly higher Factor 3 values than healthy controls (p=0.023). For patients with bipolar disorder we can expect a decrease in ETSC and physiological respiration in intact platelets, and a decrease in DMP, nonphosphorylation respiration and initial respiration in permeabilized platelets.

We also explored the duration period between the acute state and remission and its dependence on the mitochondrial pathology indicators in patients within different phases of bipolar disorder.

We calculated multiple linear regression equation for the patients in manic state (2):

$$T_{rem} = -56{,}3 + 2{,}1*X_{CS} - 4{,}8*X_{CIV} + 1745{,}1*X_{PR} - 1475{,}4*X_{ETSC} + 386{,}5*X_{Glu} \quad (2)$$

where

T_{rem} – time period between the measurements (days),

X_{CS} – citrate synthase ($nmol \cdot min^{-1} \cdot mg^{-1}$),

X_{CIV} – Complex IV ($nmol \cdot min^{-1} \cdot mg^{-1}$),

X_{PR} – physiological respiration ($pmol \cdot sec^{-1} \cdot 10^{-6}$ platelets),

X_{ETSC} – electron transport system capacity ($pmol \cdot sec^{-1} \cdot 10^{-6}$ platelets),

X_{Glu} – respiration after the addition of glutamate ($pmol \cdot sec^{-1} \cdot 10^{-6}$ platelets).

The function was statistically valid (p=0.025), the Pearson correlation coefficient for the relationship between the mitochondrial function indicators and remission due date was r_{xy} = 0.769, which shows a high closeness of relationships according to Chaddock scale. The regression model (2) explains 59.1% of the variance for the remission due date in patients with manic episode of the bipolar disorder.

There was no valid model showing the remission due date dependence of the mitochondrial function indicators for patients with a depressive episode of the bipolar disorder.

5. Diskuse

The current study contributes to the research on the connection between pathophysiological processes in mitochondria and psychopathological symptoms in different mental disorders.

One study was focused on finding biological markers of mitochondrial dysfunction measurable in peripheral blood (Fisar Z, Raboch J, 2008). Elements isolated from the peripheral blood, especially platelets and lymphocytes, are used to study changes in biochemical processes caused by mental disorders. Though mitochondrial pathology may not be similar across all brain regions and cell types, nor a number of neurochemical parameters, this is an acceptable model reflecting changes in the CNS because isolating blood platelets doesn't require a complicated and invasive procedure. Affected mechanisms of the cellular compensation can lead to an increased ETS activity in lymphocytes as they provide the energy for the cell, and, in turn, a low platelet sensitivity may be expected (Feldhaus P et al, 2011).

We found that CI, CII and CS activity in BPD patients with mania and depression were not statistically different. These findings are in conjunction with results of previous investigations. Gubert made study where the activities of ETS