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The project of experimental testing of the hypothesis regarding the effect of sodium phenylbutyrate for reducing dopamine depletion in the brain in Lesch-Nyhan syndrome using new personalized genetic HPRT1-deficient mouse as a pharmacological model

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Lesch-Nyhan syndrome is an X-linked inborn error of purine metabolism which is caused by mutations in the HPRT1 gene encoding the purine recycling enzyme hypoxanthine-guanine phosphoribosyltransferase (HPTR), the prevalence is approximately 1:380000. The disease manifests during the first year of life and is characterized by uric acid overproduction and urate nephropathy combined with severe neurologic dysfunction including cognitive impairment, dystonia, choreoathetosis, spasticity and self-injurious behavior. Overproduction of uric acid is controlled well with allopurinol. But until now, there is no sufficiently effective pharmacologic therapy for neurologic dysfunction in Lesch-Nyhan syndrome. We hypothesized that HPRT deficiency leads to hyperactivation of guanine deaminase (GDA), which has the same localization and expression levels in the brain as HPRT. GDA irreversibly converts guanine to xanthine with the release of ammonia. Local excess of ammonia in brain structures triggers a cascade of pathological processes resulting in impaired transport and release of dopamine in the nigrostriatal pathway, hyperactivation of the NMDA receptors and combined hyperactivation of adenosine and dopamine receptors, neuronal insensitivity to exogenous dopamine. We offer to test the effect of ammonia binding remedy Sodium Phenylbutyrate for reducing dopamine depletion in the brain. To test this hypothesis, we created a new personalized genetic HPRT1-deficient mouse model. We used the CRISPR-Cas9 genomic editing system to introduce the deletion of 8Val in the first exon of the HPRT1 gene in the mouse model. This hemizygous mutation is the cause of Lesch-Nyhan syndrome in one of the patients observed in our clinic. Despite the fact that Hprt-deficient mice do not demonstrate a clinical complex characteristic of patients with Lesch-Nyhan syndrome, they have depletion of dopamine in the same brain structures. These models should be used in studies of brain metabolism and preclinical studies of the effectiveness of new treatments for this disease.

Recent Publications :

1. Fu R., Jinnah H.A. (2011) Genotype-phenotype correlations in Lesch-Nyhan disease: moving beyond the gene. Journal of Biological Chemistry 287(5): 2997–3008.
2. Torres R.J., Puig J.G. (2007) Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet Journal of Rare Disseases 2: 48.
3. Fairbanks L.D., Jacomelli G., Micheli V., Slade T., Simmonds H.A. (2002) Severe pyridine nucleotide depletion in fibroblasts from Lesch-Nyhan patients. Biochemical Journal 366(Pt 1): 265–272.
4. Deutsch S.I., Long K.D.B., Rosse R.B., Mastropaolo J., Eller J. (2005) Hypothesized deficiency of guanine-based purines may contribute to abnormalities of neurodevelopment, neuromodulation and neurotransmission in Lesch-Nyhan syndrome. Clinical Neuropharmacology 28: 28–37.
5. Meek S., Thomson A.J., Sutherland L., Sharp M.G., Thomson J., Bishop V., et al. (2016) Reduced levels of dopamine and altered metabolism in brains of HPRT knock- out rats: a new rodent model of Lesch-Nyhan Disease. Scientific Reports 6: 25592.

6. Bayat A., Christensen M., Wibrand F., Duno M., Lund A. (2015) Mild Lesch–Nyhan Disease in a Boy with a Null Mutation in HPRT1: An Exception to the Known Genotype–Phenotype Correlation. JIMD Reports 18: 135- 137.
7. Kosenko E., Montoliu C., Giordano G., Kaminsky Yu., Venediktova N., Buryanov Ya., Felipo V. (2004) Acute ammonia intoxication induces an NMDA receptor-mediated increase in poly(ADP-ribose) polymerase level and NAD+ metabolism in nuclei of rat brain cells. Journal of Neurochemistry 89: 1101-1110.
8. Göttle M., Prudente C.N. Fu R., Sutcliffe D., Pang H., Cooper D., Veledar E., et al. (2014) Loss of dopamine phenotype among midbrain neurons in Lesch-Nyhan disease. Annals of Neurology 76(1): 95-107.
9. Rice M.E. (2011) H2O2: a dynamic neuromodulator. The Neuroscientist 17(4): 389-406.

Biography

Maria I. Yablonskaya has passion in clinical genetics and especially in diagnostics and management of inherited metabolic diseases.

Notes: