

Jolanta Sykut-Cegielska

ADVANCES IN TREATMENT OF RETT SYNDROME

POSTĘPY W LECZENIU ZESPOŁU RETTA

Screening Department, Institute of Mother and Child, Warsaw, Poland

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Rett syndrome (MIM #312750) is a neurodevelopmental disorder, which is caused primarily by mutations in a transcriptional regulator, methyl CpG-binding protein 2 (MECP2) and affects approximately 1 in 10,000 live female births and is the second most common cause of severe mental retardation in females [1]. Until now only symptomatic treatment has been recommended. But as in other diseases presenting with abnormal neurodevelopment, therapeutic options have been very limited. Nowadays fortunately, development of modern genetic technologies in molecular biology allows trying new concepts and therapeutic methods also in Rett syndrome. The advances in the basic science of the disease pathomechanism, and particularly a development of mouse models enable experimental preclinical studies on novel therapies. Though it is obvious that the animal is not the same as the human body, animal studies are important for better understanding of pathophysiology and for testing new interventions. In the potential currently ongoing therapies at the preclinical investigation phase some pharmacological compounds are tried. Among them such as neurotrophin family of growth factors (brain-derived neurotrophic factor - BDNF and BDNF-Mimetics), which play significant role in neuronal differentiation and survival in early development and also a strong modulator of synaptic transmission and plasticity in the mature brain [2]. Beneficial effect of these growth factors (as well as of Insulin-like Growth Factor-1) has been proved in terms of reversing and attenuating the Rett syndrome phenotypes in MECP2 mutant mice. Another pharmacological approach, which nowadays has been a topic of several studies, is aimed toward overcoming transcriptional termination caused by nonsense mutations [3]. The patients with Rett syndrome due to such mutations present with severe clinical picture. For them so-called read-through compounds like: aminoglycosides antibiotics or other small molecules, which may reverse the phenotypes (in cell lines of Rett syndrome, at least), could be a possible therapeutic option.

Few months ago new promising results obtained from the study using MECP2-null mice, have been published. They revealed that targeting N-methyl-D-aspartate (NMDA) receptors (through using NMDA receptor antagonist, ketamine) can be a safe and effective treatment for Rett syndrome; mainly regarding extension of life span and vision improvement [4].

Recently, the research group of Nicholas Tonks from Cold Spring Harbor Laboratory published the results of their long-lasting (over 25 years) study on the enzyme called PTP1B [5]. PTP1B is protein tyrosine phosphatase encoded by PTPN1 gene, which increased level was detected in murine model of Rett syndrome. It becomes possible candidate for therapy due to a rather complicated mechanism. PTP1B appeared to negative influence tyrosine phosphorylation of the tyrosine kinase TRKB, the receptor for BDNF. So inhibition of PTP1B led to increased tyrosine phosphorylation of TRKB in the brain, which would augment BDNF signaling. Tonks and his coworkers showed that pharmacological inhibition of PTP1B ameliorated the effects of MECP2 disruption in mouse models of Rett syndrome, including improved survival in young male (MECP2-/y) mice and improved behavior in female heterozygous (MECP2-/+) mice. Such promising results may become in future an effective therapeutic strategy for the patients with Rett syndrome.

REFERENCES

1. Chapleau CA, Lane J, Pozzo-Miller L, Percy AK. Evaluation of current pharmacological treatment options in the management of Rett syndrome: from the present to future therapeutic alternatives. Curr Clin Pharmacol. 2013;8(4):358-369.
2. Amaral MD, Chapleau CA, Pozzo-Miller L. Transient receptor potential channels as novel effectors of brain-derived neurotrophic factor signaling: potential implications for Rett syndrome. Pharmacol Ther. 2007;113:394-409.
3. Rowe SM, Clancy JP. Pharmaceuticals targeting nonsense mutations in genetic diseases: progress in development. BioDrugs. 2009;23:165-174.

4. Patrizi A, Picard N, Simon AJ, Gunner G, Centofante E, Andrews NA, Fagiolini M. Chronic Administration of the N-Methyl-D-Aspartate Receptor Antagonist Ketamine Improves Rett Syndrome Phenotype. Biol Psychiatry. 2015 doi: 10.1016/j.biopsych.2015.08.018. [Epub ahead of print]
5. Krishnan N, Krishnan K, Connors CR, Choy MS, Page R, Peti W, Van Aelst L, Shea SD, Tonks NK. PTP1B inhibition suggests a therapeutic strategy for Rett syndrome, J Clin Invest. 2015;3;125(8):3163-177.

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Address for correspondence:
Jolanta Sykut-Cegielska
Screening Department Institute of Mother and Child
ul. Kasprzaka 17A, 01-211 Warsaw
tel. (+48 22) 32-77-375
fax: (+48 22) 32-77-375
e-mail: jolanta.cegielska@imid.med.pl