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# Antipsychotic activity of a new PTPN5 blocker (TC-2051) in mice with the Disc1-L100P mutation

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*Motivation and Aim*: Schizophrenia is a serious disabling mental disorder that, according to WHO, affects more than 20 million people worldwide [1]. The heterogeneity of the disease and frequent resistance to the therapy used often leads to ineffective or side-effect therapy and sometimes a combination of drugs may be the best choice – this also increases the number of adverse reactions. This presents a challenge for the search for new drugs in the treatment of schizophrenia [2, 3]. The main effect of AP is associated with a decrease in dopamine, however, the modern pharmacology trend is a point effect on the key links in the pathological process. Of interest is the STEP enzyme (striatal-enriched protein tyrosine phosphatase) encoded by the *Ptpn5* gene *(protein tyrosine phosphatase non-receptor type 5)*. STEP has two isoforms, cytosolic STEP46 and membrane STEP61, which are highly expressed in the striatum, while only STEP61 is present in the hippocampus and cortex. This phosphatase, being expressed in dopaminergic neurons, is involved in signaling along the ERK pathway mediated by dopamine type 2 receptors (D2R), in the regulation of the development of dopaminergic neurons and, apparently, plays a role in the development of cognitive impairment [4,5]. The study of STEP blockers in models of schizophrenia as a putative AP seems to be relevant. We are screening new compounds capable of blocking STEP in Disc1-L100P mice (a genetic model of schizophrenia). The aim of this study was to evaluate the antipsychotic effects of the STEP blocker TC-2051 in a number of behavioral tests for manifestations of schizophrenia-like behavior in mice of the Disc1-L100P line.

*Methods and Algorithms*: The work was performed on 4-month-old mutant male mice of the Disc1-L100P line, and wild-type males (inbred line C57BL/6NCrl; WT). Mice were used from the National University "Biological Collection – Genetic Biomodels of Neuropsychiatric Diseases" (No. 493387) of the Research Institute of Neuroscience and Medicine [6]. Mice of the Disc1-L100P line carry a point mutation in the 2nd exon of the Disc1 gene. These mice are a model of schizophrenia and meet the criteria for models of mental disorder [7]. Testing was carried out between 9:00 and 16:00 in accordance with the PPI test protocols (using sound signals with loudness: prestimuli – 72, 78, 82, 86 dB; stimuli that cause startle response – 110 dB; background noise – 65 dB) [8], LI (sound signal loudness 80 dB, current strength 0.4 mA) [9] – the most commonly used to determine the schizophrenia-like phenotype. The effect of the drug on motor activity was assessed in the open field test [10]. The working conditions with the animals complied with international standards (Council of the European Communities Directive

86/609/EES). The preparation TC-2051, synthesized at the Novosibirsk Institute of Organic Chemistry, was intraperitoneally administered to mice at a dose of 10 mg/kg (which showed the most pronounced effect for the TC-2053 compound) 30 minutes before the start of testing. There were from 7 to 10 males in each group.

*Results*: The introduction of TC-2051 reduced locomotor activity in the open field in mice of both genotypes in comparison with the WT, which brought the value of Disc1-L100P closer to that of the wild type without the drug. Disc1-L100P mice showed a reduced PPI relative to WT and the introduction of TC-2051 slightly increased this indicator in them at prestimulus volumes of 82 and 86 dB. It is noteworthy that after administration of the drug, PPI in Disc1-L100P mice at 86 dB became indistinguishable from the values in the wild type. In LI test were found differences between the groups of Disc1-L100P mice with and without pre-exposure against the background of TC-2051 administration, which is typical for wild type mice.

*Conclusion*: The results obtained indicate the prospects for the use of STEP-blocking compounds of a number of benzopentathiepines as new antipsychotics.

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