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Effect of chronic unpredictable mild stress on stress resilience in Disc1-Q31L mice

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Motivation and Aim: Mental illness in the modern world is an extremely common phenomenon, according to 2017 data, about 970 million people around the world suffer from them [1]. Adverse life events and stress are the main predictors for its development, especially in individuals genetically predisposed to these diseases [2]. Based on preclinical and clinical studies, it has been conceptualized that depression has complex etiology, including gene x stress interactions.. The chronic unpredictable mild stress (CUMS) protocol is an established method for modeling depression-like behavior in animals [3]. It is also known that CUMS increases the amount of DISC1 protein in the hippocampus [4]. At the same time, the lack of the DISC1 protein leads to the degradation of the BMAL1 protein, which has been shown to be involved in stress responses and mood disorders [5, 6]. Disc1-Q31L$^{-/-}$ mutant mice showed mood-related phenotypes [7] and, hence, study of the molecular mechanisms of Disc1-Q31L x CUMS interactions would facilitate understanding of the pathogenesis of depression.

Methods and Algorithms: In this study were used male mice of two lines C57BL/6 and Disc1-Q31L$^{-/-}$ at the age of 2–3 months. Animals were maintained under four week CUMS conditions, in accordance with previously published protocols [3]. Intact animals of both genotypes were used as comparison groups. Behavior was assessed in forced swimming (FS) and open field (OF) tests [7]. To assess the effect of a *Disc1* gene mutation on the amount of BMAL1 protein, the method of immunohistochemical analysis on frozen sections (IHC) was used. Micrographs were analyzed using the Image Pro-plus 6.0 software. Statistical analysis was performed using the STATISTICA program. For samples with a normal distribution, ANOVA analysis of variance was used, followed by post-hoc analysis by Fisher's method.

Results: The result of two-way ANOVA analysis showed a significant influence of the CUMS factor [$F(1.30) = 55.105$; $p < 0.0001$], which caused pronounced depression-like behavior in C57BL/6 mice in the FS test (LSD, $p<0.0001$), in addition, the interaction of genotype and stress factors was shown [$F(1,30) = 43.518$; $p < 0.0001$]. At the same time, no changes in motor activity were observed in the OF test. CUMS did not affect the behavior of Disc1-Q31L$^{-/-}$ mice in these tests (Fig. 1, A, B). Thus, a mutation in the Disc1 gene prevents the occurrence of a behavioral response to CUMS. One-way ANOVA analysis of the IHC study results showed that in intact Disc1-Q31L$^{-/-}$ animals, there was a significant increase in the amount of BMAL1 protein in the areas of the dentate gyrus and CA3 areas of the hippocampus (LSD, $p < 0.05$). (see Fig. 1, C, D).

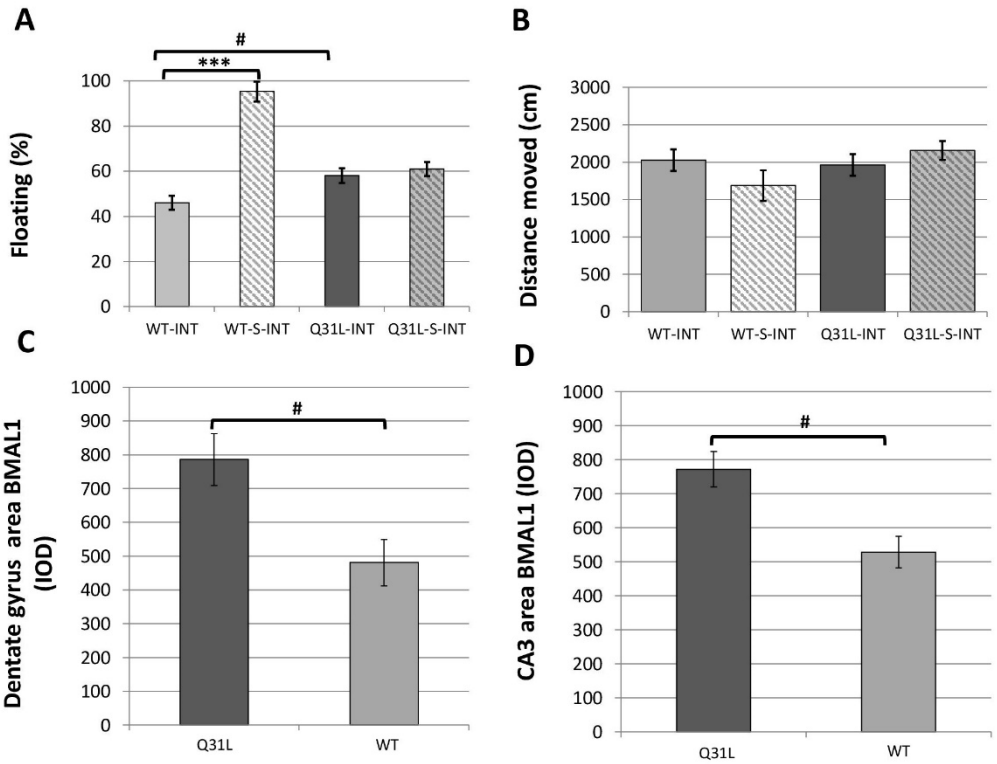

Fig. 1. Effect of *Disc1* mutation. A – floating time in FS test. B – distance moved in OF test. C, D – IHC results, illuminance optical density (IOD). $^{*,\#}p < 0.05$, $^{***,\#\#\#}p < 0.0001$

Conclusion: In the study was found that DISC1 plays an important role in the response to chronic stress. Disruption of its structure leads to increase in the amount of BMAL1 protein in the hippocampus, which likely prevents progression of abnormal behavior in response to CUMS.

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