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Role of Ribosome biogenesis in Autism.

Autism spectrum disorder (ASD) is a group of disorders characterized by social communication deficits and increased repetitive behaviors. However, the molecular pathway underlying the pathology of ASD is still unknown. Decreased neuronal cellular volume (nucleolar and cytoplasmic) has been found in autistic children that continues through adolescence and adulthood, which has been used as a biomarker for autism. This decrease may be caused by nucleolar inactivation that reduces nucleolar activity and ribosome biogenesis, affecting neuronal size, learning & memory, sensory processing, and social behavior in ASD. The current experiments examined the role of ribosome biogenesis(de novo rRNA synthesis) in ASD. We first compared de novo rRNA synthesis levels between homecaged ASD mice model and homecaged B6 mice using qPCR. We found that rRNA synthesis was downregulated in the ASD mouse model. Next, Utilizing contextual fear conditioning (CFC), we determined the expression of learning-induced rRNA synthesis and found it downregulated.

Further, we enhanced ribosome biogenesis during contextual fear conditioning(CFC) by treating 3BDO, a non-toxic butyrolactone derivative. Upon treatment with 3BDO, we found an increase in de-novo rRNA synthesis and rescue of cognitive impairment of ASD mouse model. Similarly, enhancing ribosome biogenesis by 3BDO in ASD mice model 1 h before marble burying task and social approach could ameliorate repetitive behavior, but the social behavior was not improved. In addition, intra-hippocampal injection of the Pol I specific inhibitor, CX-5461, before training (CFC), revealed that de novo rRNA synthesis is required for 24 h memory, but not for learning. These data suggest that ribosome biogenesis plays a vital role in learning and cognition in the ASD mouse model. From a therapeutic point of view, our data represents a potential novel therapeutic target for ASD