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METABOLIC KETOSIS SUPPRESSES AUTISM-LIKE STEREOTYPIC REPETITIVE BEHAVIOR AND PROMOTES SOCIAL AFFINITY IN ASOCIAL CAVEFISH.



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Stereotypic repetitive behaviors occur in mammals and fishes, hindering complex tasks, including social interactions. These repetitive behaviors are prone to emerge under chronic stress which elevates blood glucose levels. The medical ketogenic diet feeding suppresses glycolysis while it induces ketosis, and reduces repetitive behaviors in patients with autism and autism model mammals. However, the genetic and neural mechanisms underlying this keto-effect remain unclear.

The Mexican tetra, Astyanax mexicanus, consists of cave-dwelling form exhibiting autism-like behaviors including asociality and repetitive behaviors, and surface-dwelling form with typical behaviors. Cavefish share 1,839 gene expression dysregulations (up- or down-regulations) with patients with autism, and the ketogenic diet reduced their repetitive circling while promoting social affinity. Quantitative trait locus (QTL) mapping with 350 F2 hybrids identified a single genomic locus for repetitive behavior, indicating a genetic basis. Their brain transcriptome however revealed that the keto-diet feeding only shifted a few gene expressions related to metabolism and extracellular matrix. A 3D neural activity map with phosphorylated-ERK in the cleared brains showed the whole-brain hyperactivation in cavefish, compared with surface fish, which is reduced by keto-diet feeding. These findings highlight the ketogenic diet suppresses excessive neural firing and repetitive behavior regardless of many dysregulated genes.

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