Forebrain Deletion of Zc3h10 Drives a Sex-Specific "Metabolic Freezing" Phenotype with Mitochondrial Defects

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Mitochondrial homeostasis is essential for the high energetic demands of synaptic transmission. Dysregulation of this metabolic–synaptic coupling is a hallmark of neurodegeneration. We previously identified Zinc finger CCCH-type containing 10 (Zc3h10) as a mitochondrial regulator in peripheral tissues. However, the brain-specific roles of such peripheral regulators remain unexplored. Here, we report its function in the central nervous system as a potential dual regulator of mitochondrial efficiency and synaptic architecture.

Immunofluorescence in hippocampal neurons revealed that Zc3h10 is not restricted to the soma, but is localized throughout dendrites and the post-synaptic density, suggesting a direct role in synaptic function.

To investigate the neuronal function, we generated a conditional knockout mouse model lacking Zc3h10 in forebrain excitatory neurons (*Camk2a*-Cre; *Zc3h10* fl/fl). While young mice were asymptomatic, 6-month-old male knockouts developed hypoactivity, increased corner time, and severe freezing episodes in the Open Field test. Indirect calorimetry revealed metabolic inefficiency: despite reduced locomotion, males exhibited elevated oxygen consumption and energy expenditure. This indicates systemic mitochondrial uncoupling. Female mice were protected, likely via a compensatory shift toward glycolysis.

To identify the underlying mechanism, we analyzed Zc3h10-depleted neuroblastoma cells. Seahorse analysis demonstrated impaired mitochondrial respiration, accompanied by reduced protein expression of Complex I, III, and IV subunits. Transcriptomic profiling confirmed this dysfunction via downregulated supercomplex assembly factors (*COX7A2L*) and synaptic vesicle markers (*SYNPR*, *SNCA*).

These findings define Zc3h10 as a novel neuro-metabolic regulator. Its loss disrupts the balance between mitochondrial supply and synaptic demand, leading to a sex-specific phenotype of metabolic inefficiency and hypoactivity.