Key Genetic Drivers of Volitional Physical Activity in the Central Nervous System

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ABSTRACT

Previous studies suggest that physical activity is driven by the Central Nervous System (CNS). **PURPOSE**: We determined the central genetic drivers of volitional activity in the CNS and identified several molecular mechanisms promoting improvements in metabolism as a consequence of daily exercise. **METHODS**: Leveraging genetic diversity, we studied 100 strains of sedentary (SED) and exercise-trained (TRN; in cage running wheels) animals of the UCLA hybrid mouse diversity panel (HMDP). Candidate gene identification analysis and single-cell RNA sequencing in three brain regions (hypothalamus, hippocampus, and striatum) were performed. Differential gene analysis was conducted between a cohort of exercise-trained and sedentary C57BL/6J mice using the same exercise training protocol as employed for the exercise HMDP. **RESULTS**: The hypothalamus contained the highest number of candidate genes associated with volitional activity (n=81), followed by the striatum (n=56), and the hippocampus (n=41), with many driver transcripts being shared among all three brain regions. Seventeen distinct cell populations were identified within the hypothalamus, and significant differences in cell-specific transcripts were identified in TRN vs SED mice (FDR<0.05). Interestingly, expression of mt-Rnr2, which encodes the neuroprotective and anti-diabetic mitochondrial peptide *Humanin,* was significantly increased in nearly all cell types. **CONCLUSION**: Volitional activity appears significantly controlled by the genetic architecture of the hypothalamus, striatum, and hippocampus brain regions. Transcript signatures within the various cell types of these brain regions were altered following 30 days of exercise training. Our findings show that the gene encoding the mitochondrial peptide *Humanin* is exercise responsive, induced by exercise training in all three brain regions examined, and is a likely mediator of exercise-induced neuroprotection.