Dietary protein restriction disrupts hypothalamic neurogenesis in fetal rats

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Title presentation

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Abstract SNE2024 Pieter Vancamp – 2500 characters espaces inclus

Fetal programming refers to the concept that suboptimal conditions during early life predispose individuals to non-communicable diseases in adulthood. Epidemiological studies have linked inadequate protein availability for the fetus to an elevated risk of metabolic disorders, although the mechanistic origins remain elusive. We hypothesized that this risk could stem from anatomical anomalies originating during prenatal development of the hypothalamus, a brain region that governs energy balance and food intake. We subjected pregnant rat dams to either a standard diet containing 20% protein or a severely protein-restricted isocaloric diet (4%) including a 4-week pre-conceptional protein restriction of 8%. We focused on two time points within the 22-day in utero period: gestational day 15 (G15), characterized by a peak in neurogenesis, and G17 when neuronal subtypes emerge. Dams and fetuses on the low-protein diet gained less weight, indicative of intrauterine growth restriction. Single-cell RNA-seq on hypothalamic progenitors dissected from G15 fetuses and grown in culture, allowed us to identify hypothalamic neuronal subtypes and assess the impact of protein restriction. We detected 500 down- and 39 upregulated genes in protein-deprived cells, associated with processes such as cell cycle regulation, cellular metabolism and apoptosis. While EdU-pulse labeling did not show altered proliferation rates at G15 in vivo, western blots revealed reduced mTOR protein, a key amino acid sensor promoting differentiation. Additionally, a population of Isl1+ cells in the single-cell RNA-Seq dataset, precursors of arcuate nucleus neurons, including POMC and NPY subtypes, was smaller and displayed downregulation of genes involved in differentiation, as confirmed by qPCR. At G17, bulk RNA-Seq on dissected hypothalami uncovered a similar pattern of predominantly downregulated transcripts, enriched in similar cellular processes observed at G15. Immunostaining substantiated reduced numbers of POMC neurons in vivo and decreased synaptogenesis. Future experiments will assess NPY neuronal differentiation and explore the methylation status of the *Pomc* promotor. Collectively, our data offer insights into how fetal protein deficiency during critical windows of hypothalamic development could lead to programmed metabolic disruptions later in life. These findings could guide revisions to dietary recommendations for pregnant women and inform strategies to prevent metabolic misprogramming.