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Abstract

Progenitor High Fat Diet multigenerationally impairs Hippocampal Neural Stem Cell Niche †

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Metabolic dysregulation harms brain health. Early-life (pre- and perinatal) metabolic stress has been demonstrated to affect central nervous system (CNS), multigenerationally affecting brain plasticity and cognitive functions in adult offsprings. . In our previous work, we reported that maternal high fat diet (HFD) impairmed synaptic plasticity, learning and memory of descendants until the third generation. Neural stem and progenitor cells (NSPCs) represent the cellular source of newborn neurons in the subgranular zone of the hippocampus, and their fate is finely modulated by metabolic signals. Epigenetic mechanisms are key factors controlling the neural fate of NSPCs and they dynamically regulate CNS development and adult neurogenesis. Here, we demonstrate that progenitor HFD altered both the proliferation of NSPCs and the hippocampal adult neurogenesis on second and third generations of progeny (F2HFD and F3HFD), leading to the depletion of neurogenic niche in the descendants. Moreover, NSPCs derived from HFD descendants showed altered expression of several genes involved in the regulation of stem cell proliferation and neurodifferentiation (i.e., Hes1, NeuroD1, Bdnf). Furthermore, maternal HFD-related metabolic stress induced a rearrangement of STAT3/5 transcription factors occurring on the regulatory sequences of NeuroD1 and Gfap genes, causing the epigenetic repression of pro-neurogenic and the activation of pro-glial differentiation genes. Collectively, our data indicate that maternal HFD multigenerationally affects hippocampal adult neurogenesis via an epigenetic inhibition of pro-neurogenic gene expression in NSPCs.

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