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Hypothalamic Injury: Fish Oil to the Rescue!

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For more than 100 years, the field of neuroscience was aligned in consensus that, unlike in other organisms, mammalian nervous systems are incapable of generating new neurons at an adult life stage. In the early 1990s however, some experts started to question the dogma after observing signs of neurogenesis in specific brain areas of adult mammals, such as the subventricular zone (1) or the dentate gyrus of the hippocampus (2). It took another decade before, in 2001, the hypothalamus was recognized as a brain area with neurogenic potential. Pencea et al. (3) used brain-derived neurotrophic factor (BDNF) to demonstrate that the hypothalamus can recruit and/or generate new neurons (3). Later, studies by Kokoeva, Yin, and Flier (4,5) corroborated this by reporting the ability of the hypothalamus to continuously generate new neurons throughout life and noted the relevance of this process for the regulation of energy balance.

The core of central nervous system feeding circuits consists of specialized neuronal subpopulations situated in the hypothalamus. These include proopiomelanocortin (POMC) and neuropeptide Y (NPY)/Agouti-related protein (AgRP) neurons, which, in response to afferent endocrine and metabolic signals such as leptin, orchestrate behavioral output and efferent signaling but also modulate synaptic remodeling to ensure systemic energy homeostasis (6). Likewise, neuronal turnover is thought to be crucial for maintaining the integrity and functionality of adult hypothalami in health and disease (7,8). Although this concept is still discussed controversially, there is increasing acceptance in the neuroscience field that hypothalamic neurogenesis may be relevant for the development of metabolic diseases. In fact, there is evidence indicating that switching to high-fat diet (HFD) feeding in mice rapidly accelerates hypothalamic cell renewal before it shuts down dramatically (9). Indeed, Velloso and others have reported that continued HFD exposure increases apoptosis of mature neurons (10,11), newly generated neurons, and dividing cells (4,7) and reduces the survival of neuronal stem cells (12), leading to an overall reduced rate of neurogenesis and synaptic inputs in the hypothalamus (4,5,7,10).

Building on these discoveries, investigators suggest being focused on targeting hypothalamic neurogenesis to promote the remodeling of feeding circuits in order to reestablish hypothalamic function in obese conditions (4,7,10). The first studies indicated that HFD-induced reduction of neurogenesis can be partially restored by caloric restriction (7) or through the use of potent neurotrophic agents, such as ciliary neurotrophic factor, that enhance hypothalamus neurogenesis and long-term body weight loss (4).

In this issue of *Diabetes*, Velloso and colleagues (13), from the University of Campinas in Brazil, report compelling data suggesting that the use of ω-3 (also known as fish oil), a polyunsaturated fatty acid (PUFA), may offer an effective way to prevent or treat HFD-induced reduction of hypothalamic neurogenesis. The authors previously reported that partially replacing saturated fatty acids (SFAs) with ω-3 in the diet led to reduced body fat mass, improved leptin, and better glucose sensitivity (14,15). They now show that this dietary intervention also specifically increases neurogenesis and the number of dividing cells in the arcuate and the paraventricular nuclei of the hypothalamus. Furthermore, they show that central administration of docosahexaenoic acid (DHA) or BDNF to obese mice also enhances hypothalamic cell proliferation and neurogenesis, even though DHA appears to affect different cell subtypes than BDNF. Unlike BDNF, DHA induces the generation of newborn cells from the hippocampus and affects tanycytes located in the lateral wall of the third ventricle, which strongly stain for nestin. Interestingly, recent studies reported compelling data that tanycytes in the hypothalamic median eminence generate newborn neurons that are necessary for maintaining metabolic activity in adult mice (16).

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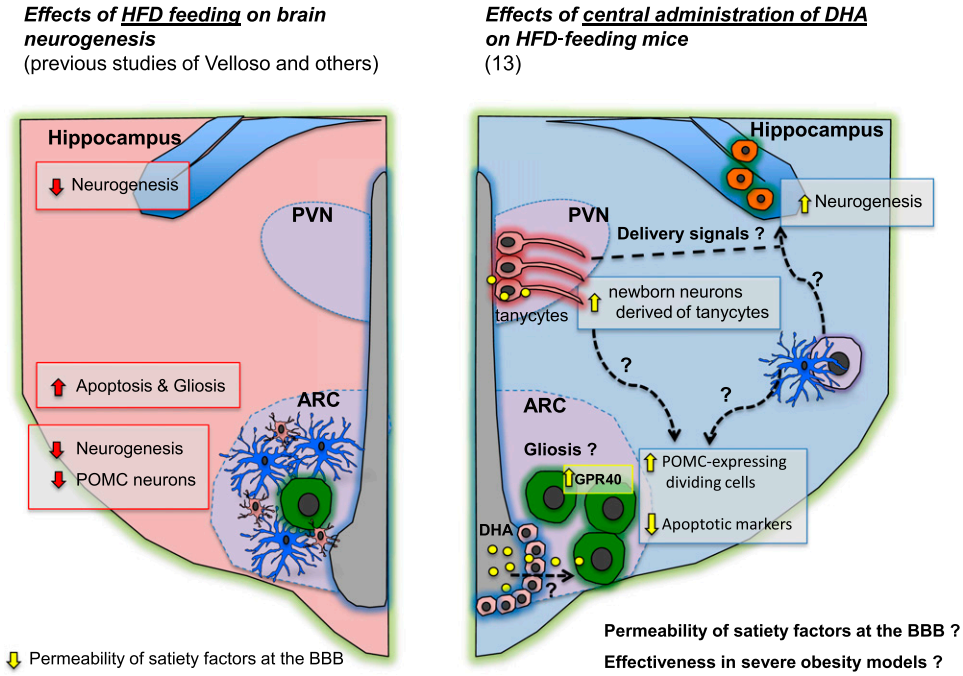

Figure 1—Schematic panel describing the effects of HFD feeding on brain neurogenesis and the benefits of DHA as proposed by Velloso and colleagues (13). Left panel: Continuous HFD feeding induces apoptosis of POMC neurons, reducing the dividing cells and newborn cells in the hypothalamus and other brain areas such as hippocampus, leading to a reduction of the overall rate of de novo neurogenesis in the brain (7,10,11,21,22). Right panel: Velloso and colleagues (13) propose PUFA interventions as a dietary tool for promoting neurogenesis, specifically in the arcuate and paraventricular nuclei of the hypothalamus and hippocampus when DHA is injected centrally. Moreover, DHA induces the proliferation of tanycytes located on the wall of the third ventricle with strong staining of nestin and increases the number of POMC neurons mediated by hypothalamic action of GPR40 that might contribute to the (re)establishment of the satiety feeding circuits to adjust the future energy balance. These relevant findings open up new questions that should be elucidated, e.g., the cellular origin of newborn neurons in the hypothalamus and hippocampus, the transport of DHA within the hypothalamus, the cell-specific expression of GPR40, and the effectiveness of DHA in neurogenesis in severe obesity models where a reduced number of stem cells with the potentiality to generate new neurons (12) and the alteration in the permeability of nutrients, such as leptin, at the blood-brain barrier (BBB) have been observed (21). ARC, arcuate nucleus of the hypothalamus; PVN, paraventricular nucleus of the hypothalamus.

Velloso and colleagues (13) therefore demonstrate the potent neurogenic effect of PUFAs on the hypothalamus, which is followed by metabolic improvements and body weight loss. This fact is not entirely surprising given that the brain is highly enriched with essential fatty acids similar to PUFAs (exclusively provided by nutrition) that regulate the fluidity and function of the cellular membranes that cover nerves (17). Likewise, some studies have claimed that an excessive intake of SFAs causes PUFA deficits in brain composition, promoting the development of neurodegenerative diseases such as Alzheimer disease (18).

Finally, Velloso and colleagues (13) report that the effects of DHA on increasing hypothalamic neurogenesis appear to be due to preferential enhanced neurogenesis of POMC (but not NPY/AgRP) neurons. This process is mediated by the activation of hypothalamic G-protein–coupled receptor 40 (GPR40). Recent studies of Velloso and colleagues (14) also have reported anti-inflammatory effects of ω-3 fatty acids in both the brain and peripheral tissues, which are mediated through the actions of GPR120 and GPR40. They show that the activation of these receptors by ω-3 fatty acids can reverse inflammation and insulin resistance in obese mice (15). Clinical trials focusing on pharmacological targeting of GPR40 have also demonstrated that GPR40 is capable of stimulating insulin secretion and lowering blood glucose levels (19).

In summary, this important work by Velloso and colleagues (13) provides ample evidence that PUFAs exert many positive benefits by preferentially promoting neurogenesis of POMC neurons and thereby reprogramming satiety feeding circuits. Further studies, however, should be performed to uncover how long-lasting the beneficial effects of PUFAs may be and to what degree their effectiveness is dependent on the level of obesity at the time of treatment initiation (Fig. 1). The endogenous capacity of the hypothalamus to restore its POMC neuronal population might continue to decline with continued exposure to HFD and increased fat mass up to a "point of no return." Indeed, the fact that long-term exposure to HFD reduces the number of adult stem cells with the potential to generate new neurons in the hypothalamus (12) would diminish the effectiveness of future dietary interventions and the chance to regenerate lost neurons. Likewise, it has

been shown that using a genetic model to rescue POMC neurons in an attempt to normalize a body weight set point failed in obese mice and was only efficient in mice that had not undergone excessive body weight gain in the past (20). Maybe even more importantly, long-term exposure to HFD alters the permeability of the blood-brain barrier, thereby restricting the access of key nutrient signals, such as leptin, to the hypothalamus (21). Such altered afferent information flow likely decreases the efficiency of dietary interventions and could explain why Velloso and colleagues (13) observe more pronounced effects of PUFAs following intracerebroventricular infusions.

Nevertheless, the elegant series of studies performed by Velloso and colleagues (13) significantly improves our understanding of cellular and molecular mechanisms governing adaptive programming of hypothalamic neural circuits. Targeted delivery of key nutrients, along with protection from detrimental dietary exposure, might offer ways to tip the balance in favor of a healthy metabolism. Additional pharmacological targeting of the hypothalamic GPR40 could help to specifically restore or even enhance neurogenesis of POMC neuron populations and thereby offer lasting prevention from diet-induced obesity and type 2 diabetes. Although mechanistic details will require in-depth studies combining next-generation targeted mouse mutagenesis with advanced stem cell methodology and cutting-edge metabolism research, we will (re)start supplementing our diet with some fish oil and hope to grow some more (of the right) neurons.

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