Mitochondrial Dysfunction in the Brain

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Inadequate energy production from mitochondria in neurons can lead to suboptimal signal transmission within the brain and other peripheral organs involved in energy homeostasis.

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1. Mitochondrial Dysfunction in the Hypothalamus

Widely recognized as a classical homeostatic center, the hypothalamus located at the base of the brain comprises numerous nuclei including the arcuate nucleus, ventromedial nucleus, dorsomedial nucleus, and paraventricular nucleus, all of which collectively regulate energy homeostasis [1]. The hypothalamus serves as an integrative energy sensor by detecting a number of nutrients and related hormonal signals from the periphery, and integrating this information with other brain inputs in order to express highly orchestrated responses via endocrine, autonomic, and behavior effectors [2].

Adequate energy production from mitochondria in neurons (as with other cell types) is crucial for optimal signal transmission within the brain and to peripheral organs in order to maintain energy homeostasis [3], so it is not surprising to find hypothalamic mitochondrial dysfunction in obesity. Among other important proteins, mitofusin 2 (Mfn2) is a GTPase located in the outer membrane of the mitochondria, and it plays a vital role in mitochondrial fusion that enables sharing essential components within the mitochondrial population [4]. Carraro and colleagues have recently shown that Mfn2 is substantially decreased in the hypothalamus of high-fat diet (HFD)-induced obese mice [5]. This may reflect an early, initial stage in obesity development because just 4 days of HFD feeding in the absence of significant weight gain was enough to downregulate hypothalamic Mfn2 mRNA [6]. Importantly, virus-mediated overexpression of Mfn2 in the arcuate nucleus of diet-induced obese mice effectively reduced body weight, adiposity, and food intake, indicating that hypothalamic Mfn2 underlies metabolic alterations and thus may be a critical element in the central regulation of energy balance [6]. In regards to potential underlying mechanisms, it is conceivable that the reduced Mfn2 expression results in unhealthy mitochondria that would ultimately lead to impaired neuronal signaling/functions and communication.

1.1. Melanocortin System in the Hypothalamus (MSH)

The melanocortin system in the hypothalamus during obesity appears to be directly affected by mitochondrial dysfunction. It consists of several key neuronal populations localized in the arcuate nucleus, namely, agouti-related protein (AgRP)/neuropeptide Y (NPY), and proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript(CART) neurons [1]. These neurons are able to sense nutrients and related hormones such as leptin and insulin depending on the nutritional status. During the fed state, α-melanocyte-stimulating hormone (α-MSH) is released from POMC/CART-expressing neurons that bind to melanocortin receptor 3 and 4 (MC3/4R) to suppress feeding and increase energy expenditure. On the other hand, upon fasting, neuropeptides AgRP and gamma-aminobutyric acid (GABA) are released from AgRP/NPY-expressing neurons to bind to MC4R and inhibit POMC neurons, respectively, thereby stimulating feeding and lowering energy expenditure [1][7]. Considering their pivotal role in the control of energy balance, the failure of mitochondrial function in these neurons is expected to disrupt neuronal processing and transmission so as to likely promote appetite and weight gain. After first observing that Mfn2 expression was significantly and consistently decreased in the hypothalamus of mice in response to HF feeding from 4 days up to as long as 12 weeks, Schneeberger and colleagues [6] demonstrated that Mfn2 deletion selectively in POMC neurons caused severe obesity that was accompanied by impaired post-translational POMC cleavage into α-MSH. At the cellular level, the lack of Mfn2 in POMC neurons decreased the activity of Complex I of the ETC and elevated ROS production leading to ER stress, suggesting that impaired mitochondrial fusion may promote a series of events conducive to the interference of the melanocortin system and induction of oxidative stress, resulting in obesity. On the other hand, mice lacking Mfn2 specifically in AgRP neurons do not display any morphological or molecular signs of ER stress or inflammation in the hypothalamus, and they are surprisingly resistant to HFD-induced obesity [8]. Interestingly, they stay leaner compared to HFD-fed wildtype controls

in spite of lowered POMC expression. While the role of mitochondrial fusion in POMC vs. AgRP neurons seems to differ, both studies described here support a potential causal link between neuronal mitochondrial dynamics within the CNS melanocortin system and energy balance.

1.2. Oxidative Damage in the Hypothalamus

Consistent with the findings in POMC neurons, defects within the hypothalamic mitochondrial biogenesis have been reported in the obese state. Colombani and colleagues [9] showed that genetically obese Zucker rats display increased hypothalamic ROS content in response to a low glucose load. While mitochondria generally produce a high amount of ROS during the process of oxidative phosphorylation, key neutralizing enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) ensure that a low mitochondrial ROS level is maintained. Unfortunately, both SOD and GPx were found to be significantly decreased in the hypothalamus of obese Zucker rats and this most probably explains the increased ROS levels. These findings are also supported by more recent work by Kovačević and colleagues, which demonstrated that a fructose-enriched diet combined with variable stressors in female rats renders obesity and dramatically lowers hypothalamic antioxidant enzymes such as SOD, glutathione reductase, and catalase [10]. Specific defects within the ETC of the mitochondria also have been observed in diet-induced obesity. Ten weeks of HFD feeding in male Swiss mice resulted in increased adiposity that is associated with oxidative damage markers in the hypothalamus, including malondialdehyde and carbonylated proteins, likely due to reduced antioxidant markers such as glutathione [11][12]. Importantly, the activity of Complex I, II, and IV within the hypothalamic mitochondrial ETC was significantly impaired in the obese mice. These failing mitochondrial capacities may well contribute to the induction of inflammation leading to obesity. On the other hand, a recent study indicates that hypothalamic inflammation in fact may precede mitochondrial dysfunction in diet-induced obesity [5]. The study showed that when male Swiss mice are placed on a HFD for 7 days, the inflammatory chemokine fractalkine in the hypothalamus appears first just 3 h after exposure to HFD, followed by a significant downregulation of Mfn2 24 h post-HFD. Treating these mice with infliximab, a monoclonal antibody capable of neutralizing TNF-α, was able to restore hypothalamic Mfn2 protein levels. It is possible that hypothalamic inflammation caused by excess nutrients can disrupt proper mitochondrial functions by first activating TLR signaling pathway. This would then suppress TCA cycle activity and drive the synthesis of microRNAs that target ETC complexes [13][14][15][16]. Altogether, these studies provide strong evidence that multiple defects within the mitochondria—impaired fusion, reduced ROS-neutralizing antioxidants, and compromised oxidative phosphorylation—may be mechanistically linked to the development of obesity and related metabolic perturbations.

2. Mitochondrial dysfunction in Extra-Hypothalamic Areas

While the hyothalamus plays an important role in regulation of body weight, multiple extra-hypothalamic regions, including the prefrontal cortex, hippocampus, and striatum, responsible for emotion, reward, and executive functions, are linked to hypothalamic regulation of body weight and feeding [17]. This raises the possibility that neuronal defects caused by abnormal mitochondrial functions in these brain areas may send inappropriate signals to the hypothalamus, consequently altering or overriding the allocated hypothalamic responses to nutrient-related inputs to promote weight gain.

2.1. The Prefrontal Cortex

The prefrontal cortex is important for executing inhibitory control (e.g., resisting strong appetite impulse), and neural responses in this area are significantly attenuated in obese individuals [18][19]. Cavaliere and colleagues [20] have revealed that inflammatory and oxidative stress markers such as TNF-α, IL-1β, and malondialdehyde were significantly elevated in synaptosomes in the cortex of obese mice fed a HFD for 18 weeks compared to those in a chow-fed lean control group. Antioxidant glutathione (GSH) was found to be markedly reduced. The ratio of GSH to its oxidized form GSSG, a readout for antioxidant activity, was decreased expected in diet-induced obese mice. Consistent with this, free radical scavengers such as SOD and aconitase were significantly decreased, which most likely exerted a negative impact on mitochondrial function as evidenced by a significant reduction in mitochondrial state 3 respiration in maximal respiration capacity. These results are in agreement with the increased superoxide production and swelling—an indicator of permeability transition pore—selectively in the mitochondria within the cortex of mice fed a HFD for 16 weeks [21]. Although these studies do not establish a clear link between mitochondrial defects specifically in the prefrontal cortex and obesity, other investigators have demonstrated similar results in this specific brain area. Swiss mice rendered obese after exposure to 10–13 weeks of HFD or similar energy-dense cafeteria diet displayed suppressed activity of citrate synthase and isocitrate dehydrogenase, enzymes responsible for catalyzing critical reactions in the mitochondrial TCA cycle, and impaired Complex II activity in the prefrontal cortex [12][22][23].

2.2. Hippocampus

The hippocampus is an essential brain region in the limbic system that governs learning and memory. Our appetitive and consummatory behavior is determined by monitoring the energy availability in the body and the detection of hormonal signals and our knowledge and reward/hedonic expectancy of foods based on its quality and related contextual cues [24]. Importantly, much of this information is processed and retrieved from our memory. Thus, it has become clear that the hippocampus actively participates in the decision-making of food consumption by altering the prediction of the hedonic consequences of feeding [24]. Neuroimaging studies have shown that hippocampal volume is diminished with aberrant neural activity in obese individuals compared to lean healthy individuals [25][26][27], indicating a potential mechanistic link between hippocampal function and metabolic health. Consistent with these results, rodent studies indicate that diet-induced obesity (via HFD or high-sucrose diet) manifests impaired memory consolidation [28][29][30] that is associated with hippocampal BBB disruption [31][32], thereby potentially increasing the entry of systemic inflammatory mediators into the hippocampus. Indeed, diet-induced obese animals exhibit microglial activation, increased ROS production, and pro-inflammatory cytokines, including IL-1β and TNF-α in the hippocampus [31][32]. As shown in the prefrontal cortex, HFD feeding is likely capable of compromising ATP synthesis in the hippocampus through lowering the activity of citrate synthase in the mitochondrial TCA cycle and suppressing the activity of Complex I, II, and IV [12][23].

2.3. Striatum

It is only recently that the mitochondrial defects in other brain regions have started to receive more attention. The striatum lies in the subcortical basal ganglia and regulates reward processes and motivation. Dysfunctional dopamine and another neural signaling in this particular brain structure have been hypothesized as some of the major contributors to overeating and the development of obesity [33][34][35][36][37]. It is thus conceivable that the striatum is quite susceptible to inflammatory insult and mitochondrial stress. Mice rendered obese by 10 weeks of HFD feeding display elevated inflammatory mediators such as TNF-α and IL-1β in the striatum and the corresponding oxidative damage, as evidenced by increased carbonylated proteins and lower glutathione [12]. Notably, ETC Complex I, II, and IV activity was significantly reduced in the striatum of these mice compared to that in lean healthy mice. Consistent with these results, a more recent study by de Farias and colleagues has shown that 11 weeks of HFD feeding induces a significant weight and fat gain, and these are associated with an impaired mitochondrial respiratory chain in the striatum [23].

3. Potential Mechanism Linking Obesity and Brain's Mitochondrial Function

While the underlying mechanisms for CNS mitochondrial dysfunction in diet-induced obesity are not clear, current research points to a potential glitch in post-translational modification. NAD-dependent deacetylase sirtuin-3 (SIRT3), a soluble protein located in the mitochondrial matrix, plays a key role in vital metabolic processes including fatty acid oxidation, oxidative phosphorylation, and antioxidant defense via deacetylating mitochondrial enzymes under stress [38]. Interestingly, SIRT3 mRNA in the brain was found to be low in diet-induced obese mice [39]. Further establishing the link between SIRT3, mitochondria, and obesity, mice with SIRT3 deletion while exposed to a HFD displayed weight gain and brain protein hyperacetylation, microglial activation, neuroinflammation, and defective mitochondrial respiration that are more pronounced than those in HFD-fed obese wild-type (WT) mice [40]. Cyclophilin D (CyPD) is a chaperone protein regulated by SIRT3, and is essential for controlling the mitochondrial permeability transition pore (MPTP), the opening of which results in impaired ATP synthesis and elevated ROS production [41]. Whether or not CypD expression in the brain is elevated with a corresponding reduction in SIRT3 during obesity is unknown. It is speculated that by deacetylating and inactivating CyPD, SIRT3 may be able to protect neurons from oxidative stress by inhibiting MPTP formation that is conducive to increased ROS production and apoptosis, thereby help maintain optimal neuronal functions and energy homeostasis. In support of this concept, Devalaraja-Narashimha and colleagues have demonstrated that a global CyPD knockout (KO) confers resistance to diet-induced obesity in both male and female mice most likely via an increased energy expenditure [42]. Brain-specific or region-specific CyPD KO would be necessary to dissect its role in regulating mitochondrial function and energy balance.

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