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REVIEWS: CURRENT TOPICS

Fatty-acid-mediated hypothalamic inflammation and epigenetic programming

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Abstract

A high-fat diet is the main environmental cue that has been studied in the hypothalamus since the discovery of its connection with hypothalamic inflammation. Current evidence shows hypothalamic inflammation as a likely mechanism for the dysregulation on the homeostatic control of energy balance, which leads to metabolic alterations and obesity. Although this mechanism seems to be reversible when set during adulthood, we argue whether dietary fatty acids, during critical periods of development, could affect hypothalamic function permanently and set an increased susceptibility to obesity. We found few experimental studies that looked at programming induced by different fatty acids on the hypothalamus. They clearly showed a connection between maternal fat diet, hypothalamic inflammation and metabolic alterations in the offspring. We found that not only a high-fat diet but also a normolipidic diet with unbalanced quantities of different fatty acids produced diverse inflammatory responses on the hypothalamus. Therefore, strategies of manipulating dietary fatty acids in pregnant and lactating women may have great impact on the population's future health. However, more research is still needed on the effects of fatty acids and the hypothalamic inflammation on programming.

Keywords: Inflammation; Programming; Fatty acids; Obesity; Hypothalamus; Appetite regulation

1. Introduction

The obesity epidemic is a worldwide serious issue and is associated with leading causes of death and disabilities worldwide. Its comorbidities include type 2 diabetes, cardiovascular diseases, musculoskeletal disorders and some cancers. In 2014, statistics revealed that around 600 million people were obese in the world. In addition, children obesity has increased considerably, posing concerns on population's future health, as it is associated with psychological disorders, risk of adulthood obesity and premature deaths. It represents an economic burden for the health care system, having also negative consequences on the country's productivity and welfare [1].

Common sense on how to lose weight tells us that a negative energy balance, eat less and exercise more, does the trick. Unfortunately, this strategy has proved to be ineffective to treat obesity in the long term. Our drive to eat goes beyond willpower, and it is finely regulated by our brain, in particular, the hypothalamus. Neuroscientists are making an effort to unearth the mechanisms that corrupt the homeostatic control of satiety and appetite that leads to weight gain.

Recently, a close correlation has been found between excess of dietary fats, hypothalamic inflammation and the disruption on hypothalamic neural circuits and metabolic alterations [2,3]. This is particularly relevant when we consider that the modern diet shifted to a higher consumption of processed foods, which are rich in fat and sugar and extremely palatable.

However, some people are more prone to obesity than others, and this could be explained by not just their genes themselves but their epigenetic profile. There is evidence that maternal dietary fats can program the offspring, during critical periods of development, and modify its susceptibility to adult chronic diseases [4–7].

The objective of this review is to explore the relationship of fatty acids on hypothalamic inflammation and programming. Our hypothesis is that fatty acids could lead to hypothalamic inflammation, and it is involved in the disruption of normal appetite control, which can lead to obesity. This disruption at an early stage of development could set the susceptibility of the individual to develop noncommunicable diseases in adulthood.

2. Hypothalamic control of energy balance

The hypothalamus is a region in the brain involved in the homeostatic control of food intake and energy expenditure in response to the body's energy state, which is indispensable for survival. The mediobasal hypothalamus (MBH) is the critical area that controls energy balance. In particular, the arcuate nucleus (ARC) contains orexigenic and anorexigenic neurons counterbalancing one another to adjust energy balance. Orexigenic neurons express neuropeptide Y (NPY) and agouti- related peptide (AgRP). Together, these neurotransmitters stimulate food intake, decrease energy expenditure and prevent the anorectic action of the α-melanocyte-stimulating hormone (α-MSH). In contrast, the anorexigenic neuron

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proopiomelanocortin (POMC) expresses the cocaine- and amphetamine-regulated transcript (CART) and POMC, which is cleaved to produce α-MSH that triggers satiety and increases energy expenditure. These hypothalamic neural pathways are interconnected and have projections to other brain areas that influence motivation/reward, energy expenditure, hunger and eating behavior [8].

Neurons in the ARC are sensible to metabolic signals from peripheral tissue, such as leptin and insulin. Leptin is an essential endocrine hormone released by adipocytes, and it mediates the communication between adipose tissue and central nervous system (CNS). Leptin acts on a negative feedback regulation: adipocyte hypertrophy stimulates leptin production. Leptin binds to its receptor in the ARC, suppressing NPY/AgRP and stimulating POMC neurons, causing the end of food intake and increased energy expenditure (Fig. 1). This leads to fat oxidation and reduction in leptin production [9]. Insulin has a similar anorexigenic effect on ARC neurons as leptin [10]. However, both hormones are overexpressed in obese humans, and they display central and peripheral tissue resistance and are linked to the development of metabolic disturbances seen in metabolic diseases.

Low-grade hypothalamic inflammation induced by high-fat diet has recently been under investigation as a possible trigger of hypothalamic insulin and leptin resistance, disrupting the homeostatic regulation of hunger and satiety and altering metabolic control [3,11,12].

2.1. The association between fatty acids and hypothalamic inflammation

In 2005, De Souza et al. [11] were the first to identify hypothalamic inflammation associated with insulin resistance in rats after 16 weeks of a high-fat diet (39% of kcal from lard). Further experiments confirmed these findings and discovered that, unlike peripheral inflammation that occurs after adipocyte hypertrophy, central inflammation induced by a high-fat diet occurs only after 24 h and before weight gain is significant [13]. Therefore, the effects of a high-fat diet seem to initiate in the CNS and affect other tissues only after prolonged consumption of a high-fat diet. Thaler et al. (2012) [13] fed adult rats with a high-fat diet (54% of kcal from lard) for 20 weeks, and they saw increased food intake and weight gain in the treatment group compared to controls. Concomitantly, they found in the treated group an increased expression of proinflammatory markers in the hypothalamus after only 4 weeks on a high-fat diet, which was not seen in the adipose tissue and liver of the animals. Interestingly, these researchers also found that increases in the expression of interleukin (IL)-6, tumor necrosis factor (TNF)-α, suppressor of cytokine signaling 3 (Socs3), I-kappa-B-kinase beta and I-kappa-B kinase epsilon caused a proportionate increase in food intake during the first days. This shows a possible link between hypothalamic inflammation and enhanced energy intake even before the onset of obesity or increased accumulation of adipose tissue.

The mechanisms involved in the hypothalamic inflammation are not completely known, but recent evidence points to gliosis and direct neural injury caused by high-fat diet (high in saturated fats) [2,3,13]. Gliosis is a response of the CNS to neural injury, and it is characterized by recruitment, activation and proliferation of neural-immune cells [14]. Thaler et al. (2012) [13] found increased accumulation, activation and cell size of microglia in the ARC from mice and rats fed high-fat diet, and it positively correlated with fat mass size. Likewise, the same pattern was observed in humans; a retrospective cohort of 34 people free from abnormalities was subjected to magnetic resonance imaging. This identified the presence of gliosis in the MBH, which correlated with BMI. The molecular mechanisms participating in the activation of hypothalamic inflammation are the activation of Toll-like receptor 4 (TLR-4), induction of ER stress and activation of IKKβ [15].

Like macrophages in the periphery, microglia abundantly express TLR-4, a signal-transducing receptor that responds to saturated fats through IKKβ/NFκB pathway to release proinflammatory cytokines (such as IL-6 and TNF-α) [16,17]. TLR-4 is overexpressed in obesity, and its inhibition by intracerebroventricular (ICV) injections, with immunoneutralizing antibodies against TLR-4, brings about the

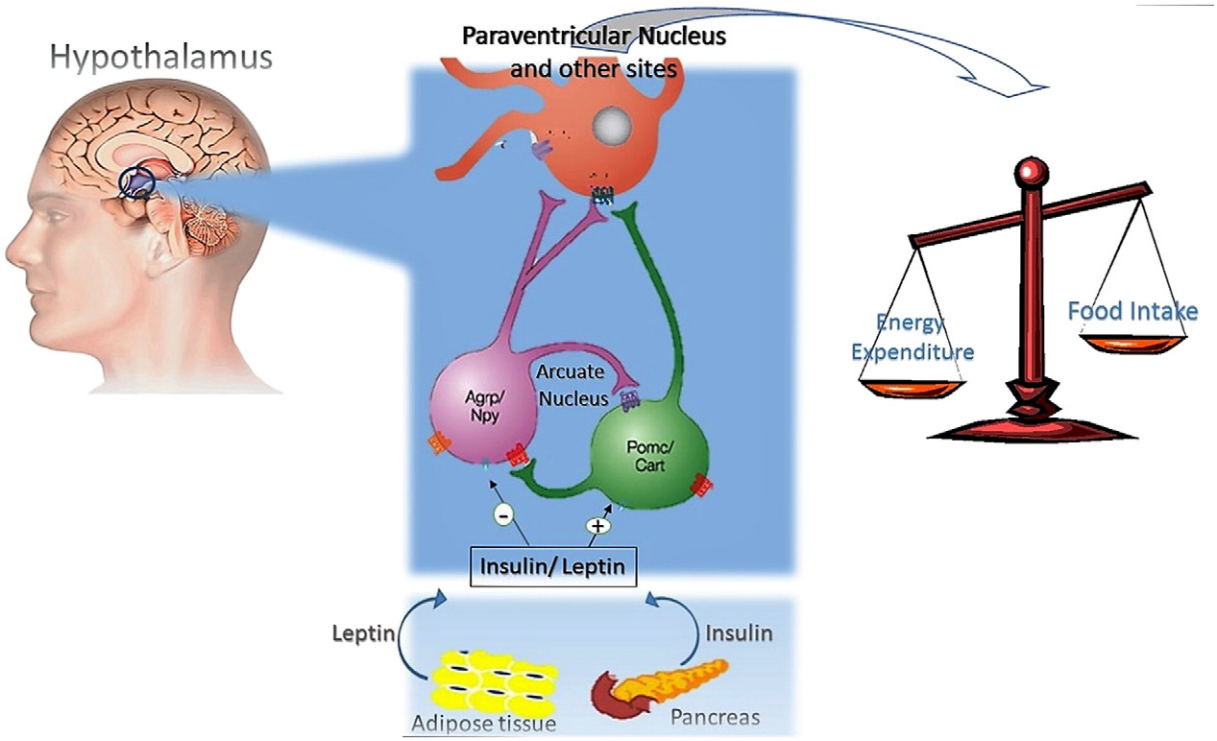

Fig. 1. Control of energy balance by hypothalamic leptin and insulin pathway. Leptin and insulin are released by the adipose tissue and pancreas respectively, on the hypothalamus; they inhibit AGRP/NPY and stimulate POMC/CART neurons. POMC/CART neurons send their projections to paraventricular nucleus and other sites and stimulate cessation of food intake and increase of energy expenditure.