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The link between hypothalamic epigenetic modifications and long-term feeding control

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ABSTRACT

The incidence of obesity, one of the main risks for type 2 diabetes and cardiovascular disease, has been rising, and changes in eating behavior are associated with this increasing rate. Body weight is maintained via a complex integration of endocrine and neuronal inputs that regulate the control of orexigenic and anorexigenic neuropeptides in the arcuate nucleus of the hypothalamus. Overfeeding may disrupt the mechanisms of feeding control, increasing orexigenic peptides such as neuropeptide Y (NPY), and/or decreasing the anorexigenic peptide proopiomelanocortin (POMC) leading to a change in energy balance and body-weight index. Despite of the great interest in this field, the mechanism by which expression of POMC and NPY is modified is not entirely clear. Over the past decades, studies have demonstrated that epigenetic modifications such as DNA methylation, histone modification and changes in miRNA dynamics, could be modulated by external stimuli and these could affect protein expression in different cells. Therefore, this review discusses the recent reports that link epigenetic modifications in the hypothalamus to changes on long-term feeding control and its role in the onset of obesity.

Contents

1. Introduction

The incidence of obesity is rising in both developing and developed countries (Guimaraes, Moura de Almeida, & Guimaraes, 2008; Lobstein et al., 2015; Nguyen & El-Serag, 2010).

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List of abbreviation

11 miRNA	micro RNA 11
5C	unmethylated cytosine
5caC	5-carboxylcytosine
5fc	5-formylcytosine
5hmC	5-hydroxymethylcytosine
5 mC	position 5 of cytosine
AgRP	and agouti-related peptide
AKT	protein kinase b
ARC	arcuate nucleus of the hypothalamus
BER	base excision repair
BMI	body mass index
CART	and cocaine-and-amphetamine regulated transcript
DA-αMSH	diacetyl alpha melanocyte stimulating hormone
DM2	type 2 diabetes
DNA	Deoxyribonucleic acid
DNMT2	DNA methyltransferase enzyme 1
DNMT3a/b	DNA methyltransferase enzyme 3a/b
H3K27me3	histone 3 lysine 27 tri-methylation
H3K4me	histone 3 lysine 4 methylation
H3K9me2	histone 3 lysine 9 di-methylation
H3K9me3	histone 3 lysine 9 tri-methylation
IRS	insulin receptor substrate
LH	hypothalamic lateral area
MBD-domain	Methyl-CpG-binding domain
miR-200	MicroRNA 200
miR-200a	MicroRNA 200a
miR-200b	MicroRNA 200b
miRNA	micro-RNA
mTOR	m- Target of Rapamycin
NPY	neuropeptide Y
ob	obese gene
PI3K	phosphoinositide 3-kinase (PI3K)
POMC	proopiomelanocortin
PVN	paraventricular nucleus
TDG	thymine-DN glycosylate
TETs	Ten-eleven-translocation
α-MSH	α melanocyte stimulating hormone

Unfortunately, this epidemic is no longer an issue that concerns exclusively the adult and elderly population. In the 21st century epidemiologic studies have demonstrated that overweight and obesity are growing among children and adolescents (Krebs et al., 2007; Lobstein et al., 2015). This increasing incidence has becoming a public health concern because obesity is one of the major risks factors for type 2 diabetes (DM2) (Santos, Tewari, & Benite-Ribeiro, 2014; Schwartz & Chadha, 2008), cardiovascular disease (Ferreira et al., 2014; Kollias et al., 2005; Steinberger & Daniels, 2003) and metabolic syndrome (Després & Lemieux, 2006; Liu, Lin, Liu, Du, & Chen, 2010), which are leading causes of death.

Overweight is defined as having a body mass index (BMI) greater than 25 kg/m^2, and obesity as having BMI greater than 30 kg/m^2 (WHO, 1995). Feeding behavior is critical to the development of overweight/obesity, thus to keep the BMI below the cut point for overweightness, the amount of energy consumed should not exceed the amount spent. Feeding control is assured through the integration of endocrine and neuronal inputs that regulate long-term food intake in both short- and long-term fashion (Woods, Seeley, Porte, & Schwartz, 1998). The arcuate nucleus (ARC) of the hypothalamus controls long-term food intake through the release of orexigenic and anorexigenic neuropeptides to the hypothalamic lateral area (LH) and the paraventricular nucleus (PVN). The release of these neuropeptides is regulated by complex pathways, and when this signaling pathway fails, overfeeding and overweightness may occur (Dhillo, 2007). Despite cutting edge research on feeding behaviors and obesity the signaling pathways behind alterations in the control of long-term feeding behavior have not been completely characterized.

There are many events of daily life that elevate and sustain physiological activities that induce outcomes such as overeating. In this stressful situation the choice of food is often a highly palatable food or high fat food versus healthy food (Adam & Epel, 2007; Benite-Ribeiro, Dos Santos, Soares-Filho, & Duarte, 2010). The increased intake of high fat food appears to be associated with alteration of the signaling pathway that regulate appetite or long term food intake (Marco, Kisliouk, Weller, & Meiri, 2013).

A large number of studies have linked the growing prevalence of obesity with changes in nutrition and behavior (Chan et al., 2009; Pugliese et al., 2007; Santos, Ribeiro, Gaya, Appell, & Duarte, 2008; Shaw, Sicree, & Zimmet, 2010), and epigenetic modifications seem the most suitable explanation at the cellular level of how these new external changes could impair hypothalamic control on food intake. Studies have linked epigenetic modification to changes in food-intake control, however, these mechanistic studies are still incipient (Marco et al., 2013; Plagemann et al., 2009). Thus, in this article we review recent reports that analyze alterations in long-term feeding control and energy expenditure induced by overfeeding from an epigenetic perspective.

1.1. Epigenetic modification

Epigenetic modifications are long-term alterations of the “epi” (from the Greek: over, around) -genome that modify the transcriptional potential of a cell leading to changes in cell function (Holliday, 2006). Epigenetic modification can induce adaptive responses that affect protein expression and several mechanisms such as cell differentiation, cell growth and apoptosis. DNA methylation, histone modifications, and micro-RNA (miRNA) activity are the three major epigenetic mechanisms identified that regulate gene expression (dos Santos, Moreli, Tewari, & Benite-Ribeiro, 2015). In fact, the reversible nature of these modifications make the field attractive for potential epigenetic therapies against the development of obesity through targeting of long-term feeding control.

1.2. DNA methylation

DNA methylation is the addition of a methyl group on the 5 position of cytosine (5 mC), which is facilitated by DNA methyltransferase (DNMT) enzymes: DNMT1 and DNMT3a/b (Jones & Liang, 2009). This binding cooperates with the N-terminal histone to create a silenced chromatin structure (Jones & Liang, 2009; Schübeler, 2015). Once methylated, 5 mC can be converted to 5-hydroxymethylcytosine (5hmC), a reaction catalyzed by the Ten-eleven-translocation enzymes (TETs). This reaction has been suggested to promote gene expression and demethylation (Tu et al., 2015). It is hypothesized that conversion of 5 mC to 5hmC by the TET enzymes blocks the repressive DNMT and Methyl-CpG-binding