Appetite 120 (2018) 230–239

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

DNA methylation patterns at sweet taste transducing genes are associated with BMI and carbohydrate intake in an adult population

O. Ramos-Lopez [a], A. Arpón [a], J.I. Riezu-Boj [a, b], F.I. Milagro [a, c], M.L. Mansego [a], J.A. Martinez [a, b, c, d, *] on behalf ofthe MENA project

[a] Department of Nutrition, Food Science and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain
[b] Navarra Institute for Health Research (IdiSNA), Pamplona, Spain
[c] Biomedical Research Centre Network in Physiopathology of Obesity and Nutrition (CIBERobn), Carlos III Institute, Madrid, Spain
[d] Madrid Institute of Advanced Studies (IMDEA Food), Madrid, Spain

ARTICLE INFO

Article history:
Received 16 May 2017
Received in revised form
9 August 2017
Accepted 5 September 2017
Available online 6 September 2017

Keywords:
Obesity
Taste perception
Sweet taste
Methylation
TAS1R2
Dietary intake

ABSTRACT

Individual differences in taste perception may influence appetite, dietary intakes, and subsequently, disease risk. Correlations of DNA methylation patterns at taste transducing genes with BMI and dietary intakes were studied. A nutriepigenomic analysis within the Methyl Epigenome Network Association (MENA) project was conducted in 474 adults. DNA methylation in peripheral white blood cells was analyzed by a microarray approach. KEGG pathway analyses were performed concerning the characterization and discrimination of genes involved in the taste transduction pathway. Adjusted FDR values ($p < 0.0001$) were used to select those CpGs that showed best correlation with BMI. A total of 29 CpGs at taste transducing genes met the FDR criteria. However, only 12 CpGs remained statistically significant after linear regression analyses adjusted for age and sex. These included cg15743657 (*TAS1R2*), cg02743674 (*TRPM5*), cg01790523 (*SCN9A*), cg15947487 (*CALHM1*), cg11658986 (*ADCY6*), cg04149773 (*ADCY6*), cg02841941 (*P2RY1*), cg02315111 (*P2RX2*), cg08273233 (*HTR1E*), cg14523238 (*GABBR2*), cg12315353 (*GABBR1*) and cg05579652 (*CACNA1C*). Interestingly, most of them were implicated in the sweet taste signaling pathway, except *CACNA1C* (sour taste). In addition, *TAS1R2* methylation at cg15743657 was strongly correlated with total energy ($p < 0.0001$) and carbohydrate intakes ($p < 0.0001$). This study suggests that methylation in genes related to sweet taste could be an epigenetic mechanism associated with obesity.

1. Introduction

The increasing prevalence of obesity constitutes an important public health and economic issue in developed and emerging countries (Tremmel, Gerdtham, Nilsson, & Saha, 2017). Globally, it has been estimated that about 2 billion people present overweight and obesity according to body mass index (BMI) measurements (Ng et al., 2014). Obesity has a pronounced impact on morbidity and mortality since contributes to the global incidence of common chronic diseases and morbid manifestation including type 2 diabetes and cardiovascular events (Seidell, 2015). Moreover, systematic analyses have revealed that overweight and obesity cause more than 3 million deaths each year (Lim et al., 2012).

Obesity epidemic is the result of environmental influences (diet and sedentary lifestyles) promoting positive energy balances and weight gains, which may interact with a genetic predisposition (Marti, Martinez-González, & Martinez, 2008). In this sense, the increased consumption of sweet energy-dense foods is thought to be a major contributor to the rising obesity rates worldwide (Bray, 2014; Ruanpeng, Thongprayoon, Cheungpasitporn, & Harindhanavudhi, 2017). Accordingly, observational studies have shown positive relationships between sweetened beverage intake and adiposity in some cases (Woodward-Lopez, Kao, & Ritchie, 2011), but not in others (Brand-Miller, 2017). In addition, there is growing evidence about the involvement of genetic and epigenetic factors in the development of obesity and associated complications by influencing individual responses to environment (Martínez, Milagro, Claycombe, & Schalinske, 2014; Milagro, Mansego, De

* Corresponding author. Department of Nutrition, Food Science and Physiology, Centre for Nutrition Research, University of Navarra, 1 Irunlarrea Street, 31008 Pamplona, Spain.
E-mail address: jalfmtz@unav.es (J.A. Martinez).

http://dx.doi.org/10.1016/j.appet.2017.09.004
0195-6663/

Abbreviations

5-HT	serotonin
ADCY6	adenylate cyclase 6
ANOVA	analysis of variance
ATP	adenosine triphosphate
BMI	body mass index
CACNA1C	calcium voltage-gated channel subunit alpha1 C
CALHM1	calcium homeostasis modulator 1
cAMP	cyclic adenine monophosphate
ChAMP	450k Chip Analysis Methylation Pipeline
CpG	cytosine-phosphate-guanine site.
DiOGenes	Diet, Obesity and Genes Dietary trial
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
ENaCs	epithelial Na + channels
FDR	false discovery rate
FOOD4ME	Food For Me study trial
GABA	gamma-aminobutyric acid
GABBR1	gamma-aminobutyric acid type B receptor subunit 1
GABBR2	gamma-aminobutyric acid type B receptor subunit 2
GEDYMET	Genetics, dysglycemia and metabolism
HDL-c	high-density lipoprotein cholesterol
HOMA-IR index	homeostatic model assessment-insulin resistance
HTR1E	5-hydroxytryptamine receptor 1E
ICTUS	International Citicoline Trial on Acute Stroke
IP3	inositol 1,4,5-trisphosphate
KEGG	Kyoto Encyclopedia of Genes and Genomes
LDL-c	low-density lipoprotein cholesterol
LIMMA	linear models for microarray data
MENA	Methyl Epigenome Network Association project
NUGENOB	Nutrient-Gene Interactions in Human Obesity trial
OBEKIT	Nutrigenetic test for personalized prescription of body weight loss diets trial
OBEPALIP	Eicosapentaenoic Acid in Human Obesity trial
P2RX2	purinergic receptor P2X2
P2RY1	purinergic receptor P2Y1
PKD1L3	polycystin 1 like 3, transient receptor potential channel interacting
PKD2L1	polycystin 2 like 1, transient receptor potential cation channel
PREDIMED	Prevención con Dieta Mediterránea trial
RESMENA	Reduction of the Metabolyc Syndrome in Navarra-Spain trial
SCN9A	sodium voltage-gated channel alpha subunit 9
SPSS	statistical package for the social sciences
SWAN	Subset-quantile Within Array Normalization
T1R	taste receptor type 1
T1R2	taste 1 receptor member 2
T1R3	taste 1 receptor member 3
T2R	taste receptor type 2
TAS1R2	taste 1 receptor member 2
TRC	taste receptor cells
TRPM5	transient receptor potential cation channel subfamily member 5
TyG	triglyceride-glucose index
VGCC	voltage-gated calcium channels
VGNC	voltage-gated sodium channels
WC	waist circumference

Miguel, & Martínez, 2013).

In this context, taste perception may play an important role in determining food preferences and eating behaviors (Galindo, Schneider, Stähler, Töle, & Meyerhof, 2012). Thus, individual differences in the ability to detect diverse taste qualities in the oral cavity may influence appetite, dietary intakes, and subsequently disease risk (Loper, La Sala, Dotson, & Steinle, 2015). Indeed, some studies have reported differences in sensitivity, perception and implicit attitude towards certain basic tastes between obese and lean subjects (Hardikar, Höchenberger, Villringer, & Ohla, 2017; Sartor et al., 2011), although others have not found such variation (Martinez-Cordero, Malacara-Hernandez, & Martinez-Cordero, 2015; Tucker, Nuessle, Garneau, Smutzer, & Mattes, 2015). Taste perception in humans is mediated by several specialized taste receptors within taste bud cell membranes: the G-protein coupled receptor families T2R involved in bitter taste (Chandrashekar et al., 2000), and T1R implicated in sweet and umami tastes (Zhao et al., 2003); other include the channel-type receptors PKD1L3/PKD2L1 involved in sour taste (Ishimaru et al., 2006), and ENaCs regulating salty taste (Chandrashekar et al., 2010). The activation of taste receptors mobilizes cellular pathways of transmission from taste bud cells to the central nervous system involving multiple mediators and effectors (Iwata, Yoshida, & Ninomiya, 2014; Kikut-Ligaj, 2015).

To date, several common polymorphisms within taste transducing genes have been associated with dietary intakes as well as on diverse metabolic disorders and chronic diseases including obesity (Ramos-Lopez et al., 2015b, 2016a, 2016b, 2015a; Chamoun et al., 2016). However, the role of epigenetic signatures in taste perception and obesity susceptibility has not been apparently explored. Advances in the understanding of epigenetic mechanisms underlying weight control may lead to the implementation of precision intervention strategies focused on early detection, diagnosis and treatment of obesity (Goni, Cuervo, Milagro, & Martínez, 2016). The aim of this study was to investigate the correlation between DNA methylation patterns at taste transducing genes and BMI in an adult population.

2. Methods

2.1. Subjects

A nutriepigenomic analysis within the Methyl Epigenome Network Association (MENA) project was conducted in 474 adults from previous cohorts (Abete et al., 2015; Huerta, Navas-Carretero, Prieto-Hontoria, Martínez, & Moreno-Aliaga, 2015; Larsen et al., 2010; Martínez-González et al., 2014; Petersen et al., 2006; San-Cristobal et al., 2015; Santos et al., 2016; Zulet et al., 2011) which constitutes the MENA project. The study protocol was in accordance with the ethical principles of the Helsinki Declaration. Subject's data were codified to guarantee anonymity.

2.2. Study variables

Anthropometric measurement and the metabolic profile were obtained from databases of the aforementioned cohorts. BMI was calculated dividing weight in kg by height in meters squared (kg/m^2). Insulin resistance was estimated using the homeostatic model assessment-insulin resistance (HOMA-IR) index (Aller, Abete, Astrup, Martinez, & van Baak, 2011). The triglyceride-glucose (TyG) index was subsequently calculated as a predictor of diabetes (Navarro-González, Sánchez-Íñigo, Pastrana-Delgado, Fernández-Montero, & Martinez, 2016) and cardiovascular events