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LETTER TO THE EDITOR

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AIMS AND SCOPE

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REVIEW

Genes, emotions and gut microbiota: The next frontier for the gastroenterologist

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Abstract

Most medical specialties including the field of gastroenterology are mainly aimed at treating diseases rather than preventing them. Genomic medicine studies the health/disease process based on the interaction of the human genes with the environment. The gastrointestinal (GI) system is an ideal model to analyze the interaction between our genes, emotions and the gut microbiota. Based on the current knowledge, this mini-review aims to provide an integrated synopsis of this interaction to achieve a better understanding of the GI disorders related to bad eating habits and stress-related disease. Since human beings are the result of an evolutionary process, many biological processes such as instincts, emotions and behavior are interconnected to guarantee survival. Nourishment is a physiological need triggered by the instinct of survival to satisfy the body's energy demands. The brain-gut axis comprises a tightly connected neural-neuroendocrine circuitry between the hunger-satiety center, the dopaminergic reward system involved in the pleasure of eating and the gut microbiota that regulates which food we eat and emotions. However, genetic variations and the consumption of high-sugar and high-fat diets have overridden this energy/pleasure neurocircuitry to the point of addiction of several foodstuffs. Consequently, a gut dysbiosis generates inflammation and a negative emotional state may lead to chronic diseases. Balancing this altered processes to regain health may involve personalized-medicine and genome-based strategies. Thus, an integrated approach based on the understanding of the gene-emotions-gut microbiota interaction is the next frontier that awaits the gastroenterologist to prevent and treat GI disorders associated with obesity and negative emotions.

Key words: Genes; Emotions; Brain reward system; Gut microbiota; Gastrointestinal disease; Personalized medicine; Genome-based nutrition; Nutrigenetics; Food decision-making; Obesity

Core tip: Even though instincts, emotions, and behavior are evolutionary mechanisms for humans to adapt, dysfunctional genes, chronic negative emotions and gut dysbiosis are high risk factors for different diseases. A deep study of the gene-environmental interactions and the gut-bacteria consortium is a key factor that could help to understand how negative emotions are translated into disease. Physicians do not always consider that emotional factors aggravate disease progression and severity. Therefore, personalized-medicine and genomic-based nutrition strategies may aid in the prevention and reduction in the prevalence of gastrointestinal disorders associated with obesity and negative emotions.

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INTRODUCTION

One of the main functions of the human gastrointestinal (GI) tract is to sustain the natural interaction between the environment and the body's interior. From an evolutionary standpoint, a series of anatomical changes has occurred over time. For example, wider and larger teeth allowed humans to eat a greater amount of plants and fruits[1]. Also, a longer small intestine helped to digest food and absorb nutrients, while removing non-digestible molecules, toxic matter and harmful agents from the body. During this evolutionary and historical process, humans were able to survive based on this capacity to eat foliage and roots, soil, and all kinds of animals. For instance, maguey worms, ant eggs, grasshoppers and snails once served as complementary survival foods for the Mesoamericans of Mexico. Later, they became part of the staple foodstuffs in several regions of the country, and paradoxically, they are considered exotic dishes in fancy restaurants today[2].

Globally, the prevalence of GI pathologies varies according to geographical location, which in turn is linked to genetic, environmental, and sociocultural, interactions. Thus, differences in the incidence and prevalence of GI pathologies may exist between urban and rural populations. However, regardless of these variables, the most common ailments are those related to bad eating habits and those associated with psychological or emotional factors[3].

As a result of the aforementioned issues, obesity has increased remarkably worldwide, along with its concomitant GI symptoms and associated co-morbidities, including type-2 diabetes and liver diseases such as non-alcoholic steatohepatitis[4]. Obesity ranks as the number one disease in both the United States and Mexico[5,6], while the economic devastation associated with type-2 diabetes and cirrhosis represents a serious problem for health services[7]. Eating less and more exercise has been the simplest proposal for the management of obesity. However, to date, all strategies to combat obesity have failed due to lack of a therapeutic target, or the patient's lack of knowledge and poor attitude[8]. On the other hand, up to 60% of GI diseases are associated with stress[9]. A globalized world comes with high rates of stress and people with GI conditions struggle even more with anxiety, stress, and pain due to extensive lifestyle changes that have an impact on their quality of life. This unhealthy scenario leads us to ask why do patients overeat? Alternatively, why after losing weight by a harsh nutritional-medical treatment or even more often after bariatric surgery, patients relapse gaining more weight or recovering the lost weight? The answer may be related to the imbalance between the food we eat, genes and emotions.

Interestingly, the oldest records that allude to the food-body-emotion interaction is in Ayurvedic Medicine and in the theory of the balance between the natural elements documented by Chinese medicine. Both are considered precursors of the concepts defined by Hippocrates in which the mind, body and spirit are represented by the Four Humours theory: sanguine, phlegmatic, choleric and melancholic[10]. Based on this background, we may consider that the common denominator of these theories is the balance between the human body and the environment, *i.e.*, what we eat, what we feel and our behavior (emotions) according to the person's personality (genetics) or character. This balance leads to well-being, health, and happiness, while an imbalance leads to illness.

Modern or scientific medicine, as defined by the concepts derived from Descartes' scientific method, has achieved significant advances in the understanding of how our body functions, first at the macroscopic and microscopic level, then followed by biochemical-physiological aspects, and most recently at the molecular level[11]. In the last century, modern medicine has focused more on disease than on health, leading to a fragmentation of our scientific knowledge[12]. Gastroenterologists may only address the sick digestive organ, whereas the nutritionist may recommend revisions to the kinds and amounts of the food we eat, but often neither of them consider the food-body-emotion interaction.

In the same sense, the concept of intestinal flora has advanced towards the study of the composition of the intestinal microbiota, which depends precisely on our eating habits. However, genomic medicine raises the question about how the genetic (inside)-environment (outside) interaction occurs. Currently, nutrigenetics and nutrigenomics are providing knowledge on how food interacts with our genes. With this new knowledge, doctors or health professionals have a new set of molecular tools to study GI disorders and establish genome-based treatment strategies. However, the interaction between eating and emotions has been less understood, causing knowledge again to be atomized throughout other disciplines such as neurology, psychology, psychiatry and even religion, or whatever it may be that leads to a greater degree of spirituality[13].

Returning to the Hippocratic's concept, in which the balance between body, mind, and spirit is necessary for health, genomic medicine currently may explain at the molecular level how this may occur. Thus, the objective of this mini-review aims to provide an integrated synopsis of the interaction between genes, gut microbiota and emotions to achieve a better understanding of the GI disorders related to bad eating habits and stress-related diseases.

EMOTIONS, INSTINCTS AND BEHAVIOR

Emotions may be defined as mental and physical states that are generated in response to internal or external stimuli. This stimulation can arise from thought (thinking), or through the visual, auditory, somatosensory, gustatory, and olfactory senses. In the ancient times, one clear example of a stimulus that arises from thought was melancholy, described as an animic state that was present when a person yearned for their homeland and their activities or for loved ones that were no longer with them. Today, this emotion has been denoted as stress, anxiety, and depression, which arises because of various circumstances.

Both thoughts and senses can be activated by an internal or external stimulus, and the basis of this response is instinct, as an essential part of survival[14,15]. Through time, evolution establishes genetically an adaptability, given by the experience, to the surrounding environment. Eventually, through this adaptability of the human to its environment, a behavior arises, which is based on learning (cognition) and genetic adaptations[16,17]. An easy example to understand how genetic-environmental interactions modulate behavior is through the behavioral traits of different breeds of dogs, whose behavior or character is a mixture of the genetic aspects of the race and training (learning).

From Darwin to contemporary authors, emotions have been given different definitions and classifications to explain the health/disease process. However, it is worth rethinking the concept of instinct. Instincts are a set of physiological and mental reactions that lead to the preservation of life. These instincts arise from an internal or external stimulus; subsequently, the body responds by entering in a state of alert followed by a movement. In fact, emotion in Latin means "motion". Darwin states that there are different facial expressions related to that movement[18]. These physical changes are fast, specific, and self-limiting; thus, the body may return to the original state after the stimulus disappears or it may chronically persist if the emotion is not resolved, for example, a feeling of resentment.

Once the state of alert is initiated, blood flows into specific body areas depending on the situation. For example, blood flows to the legs in case of "fear", towards the chest and arms in case of "fight", and to the genitalia when a possible mate is detected or to the stomach when the appetite or hunger arises[16]. Additionally, in regard to the blood flow, Alexander Lowen suggests sorting emotions into positive or negative[19]. Positive emotions are all those that provide well-being and pleasure, while negative emotions generate the opposite. The former favors blood flow whereas the latter generate vasoconstriction, releasing adrenalin and cortisol, which activates stress. Based on Lowen's concept, one or a set of negative emotions over an extended period could lead to chronic illness. Therefore, in the medical context, a clear and integrated approach could help us to understand the role of instinct, emotions, and behavior in the health/disease process, and to establish therapeutic targets.

FUNCTIONAL GASTROINTESTINAL DISORDERS AND EMOTIONS

Functional gastrointestinal disorders (FGIDs) are a broad spectrum of chronic abnormalities, some of which arise from dysfunctional brain-gut interactions that can lead to dysmotility and hypersensitivity[20-22]. Several factors such as genetic susceptibility, gut physiology, microbiota composition, and psychological factors have been associated with FGIDs[23-25]. Episodes of anxiety and depression are experienced more frequently in individuals with FGIDs than in healthy subjects[26,27]. They also have been related to physiological changes in colonic motility, abdominal pain, mucosal blood flow and hyperreactivity among patients with intestinal bowel syndrome (IBS)[22]. Furthermore, negative emotions, stressful life events and personality traits like neuroticism have been associated with IBS, colitis, Crohn's disease (CD) and dyspepsia[28]. At the same time, impaired attention and emotion regulation elicit symptoms of anxiety, hypervigilance, and hypersensitivity[20,21].

Among patients with FGIDs, quality of life is affected in two ways: first, anxiety and depression seem to predict the presence, severity, and frequency of symptoms[29,30]; and second, GI disorders may exacerbate the presence of negative emotions[31]. In fact, overall GI functions such as hunger, appetite,

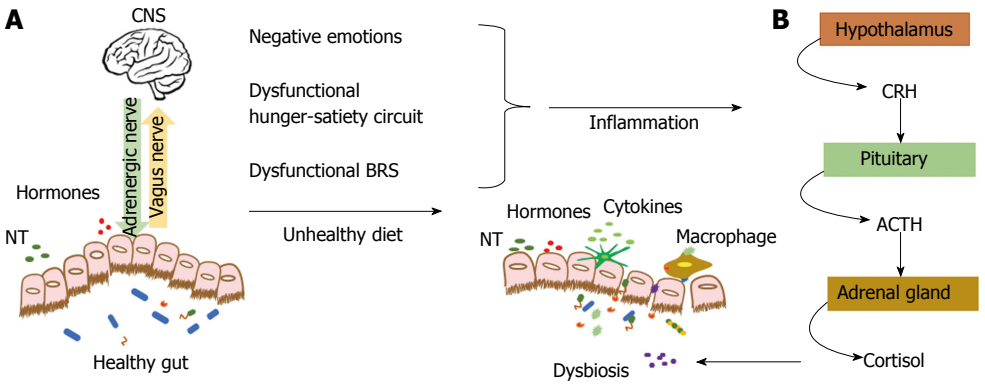

Figure 1 Gut-brain axis and dysbiosis. A: The gut microbiota maintains a two-way communication with the CNS using hormones, neuropeptides, NT, cytokines and the afferent (vagus nerve) and efferent signals (adrenergic nerve); B: Alterations in the energy balance circuit and BRS that lead to negative emotions chronically activate the HPA axis elevating cortisol levels. Cortisol results in dysbiosis, allowing pathogens to permeate the gut barrier and activate inflammation. Unhealthy dietary patterns also lead to dysbiosis, inflammation and negative emotions. CNS: Central nervous system; BRS: Brain reward system; CRH: Corticotrophin-releasing hormone; ACTH: Adrenocorticotropic hormone; HPA: Hypothalamus-pituitary-adrenal.

satiety, digestion, absorption and evacuation are affected by negative emotions[32]. However, the pathophysiological process of how emotions relate to GI disorders is not clearly understood. It has been proposed that homeostatic signals between the GI system and emotions are integrated by the gut-brain axis. This axis comprises the interaction between the endocrine, the immune and the enteric nervous systems[33], which in turn, interact with the autonomic and central nervous systems. For example, chronic stress promotes the release of pro-inflammatory cytokines and C-reactive protein. This protein stimulates the hypothalamic-pituitary-adrenal (HPA) axis by liberating corticotrophin-releasing hormone from the hypothalamus, which stimulates the activation of the sympathetic nervous system and the secretion of adrenocorticotropic hormone, which finally stimulates the release of cortisol from the adrenal cortex to limit stress[34]. In fact, patients with FGIDs and exacerbated anxiety and depression have high cortisol levels[35]. Due to HPA axis dysregulation the mesolimbic brain reward system (BRS) is altered, resulting in cognitive and emotional disturbance. As a result, FGIDs patients, predominantly IBS patients, are characterized by high rates of hypersensitivity related to GI symptoms such as pain[20].

EMOTIONS AND MICROBIOTA

The gut hosts almost 100 trillion microorganisms that share symbiotic properties with humans. Intestinal microbiota regulates part of the host's metabolic and energy balance, modulate intestinal motility, and regulate immune system maturation. Also, it confers protection against pathogens and toxins, regulates cytokines secretion from adipose tissue, insulin signaling and finally, modulates host emotions and cognition[36,37]. The gut microbiota is considered our second genome, because it constitutes 90% of the total number of cells that interact with our bodies[38].

As shown in Figure 1A, the gut microbiota can help regulate emotions and cognition because it maintains a two-way communication with the brain[39] using the nervous, endocrine and immune systems[40]. Brain-gut communication is driven by the vagal nerve, which connects to nearly 100 million neurons in the enteric nervous system together with afferent (vagal and spinal) and efferent adrenergic neurons (sympathetic and parasympathetic)[41]. Moreover, certain gut bacteria synthesize neurotransmitters[42] and close to 20 neuropeptides produced in the enteroendocrine cells (central and peripheral neurons) serve as second messengers in the brain, thus regulating mood and cognition[43]. Some of these include substance P, calcitonin, corticotropin releasing factor, pancreatic polypeptide, vasoactive intestinal polypeptide, GLP-1 and somatostatin, neuropeptide Y, and peptide YY, among others[42]. These last two neuropeptides play a major role in body energy homeostasis[44]. The endocrine system regulates the release of gut bacteria neurotransmitters[43] and ghrelin, influencing the levels of neurotransmitters such as dopamine[45] whereas the brain controls the neuroendocrine factors. Finally, adhesion molecules maintain the integrity of the intestinal mucosa, which serves as a physical and chemical barrier against pathogenic bacteria[46]. Also, antigen recognition of pathogen-associated molecular patterns are recognized by the Toll-like receptors, modulating the activation of the immune response against nocive bacteria[47].

As shown in Figure 1B, alterations of the BRS and negative emotions, together with other unhealthy lifestyle factors produce a dysbiosis, which is an imbalance between beneficial and non-beneficial bacteria[46]. As mentioned before, activation of the HPA axis[40] releases free systemic stress hormones such as adrenaline, noradrenaline, and cortisol that promote bacterial growth of pathogens such as *E. coli* (E. coli0157), *Yersinia enterocolitic*, and *Pseudomonas*

aerugins that further promote the synthesis of pro-inflammatory cytokines[43]. This scenario facilitates the loss of intestinal mucosa integrity. Lipopolysaccharides, pathogenic bacteria and toxins can permeate into the systemic circulation producing a metabolic endotoxemia[48,49]. This state generates pro-inflammatory conditions, insulin resistance and metabolic abnormalities related to chronic diseases[50].

Furthermore, a Western diet containing a high-sugar and high-fat composition contributes to dysbiosis and to a lower production of short-chain fatty acids from fiber fermentation, which have an anti-inflammatory role[51]. A high-fat diet promotes inflammation by increasing the expression of TNF-α and IL-6 inflammation-related cytokines, and macrophage infiltration[52]. Moreover, epidemiological studies have shown that central obesity and BMI are predictors of depression, anxiety and low quality of life[53,54]. Dysfunctions in adipose tissue are implicated in the development of stress and depression[55]. Adipocytes mediate a neuro-inflammatory profile affecting emotion and cognitive brain regulatory centers[56]. Also, inflammation is related to neurobiochemical alterations such as impaired serotonin synthesis, depletion of melatonin and tryptophan and neuronal damage in the hippocampus due to altered glutamatergic pathways[57]. Moreover, the prevalence of psychopathologies increases proportionally with the number of obesity-related metabolic diseases and metabolic syndrome components such as abdominal obesity, hypertriglyceridemia, and reduced high-density lipoprotein levels[58,59].

In this vein, changes in gut microbiota composition and diversity are related to immune-mediated diseases such as colitis, inflammatory bowel disease (IBD) and CD. For example, when compared to healthy subjects, patients with colitis have a reduced abundance of *Akkermansia* (phylum Veruccomicrobia), which promotes mucin degradation and protection against toxins[60]. Bacteria composition and diversity is also affected in IBD patients, who show a reduced number of Firmicutes and a higher number of Proteobacteria and Tenericutes; increases in *E. coli* populations is also associated with IBD[61]. Patients with CD tend to have a decreased number of the beneficial bacteria Firmicutes and increased number of Bacteroidetes when compared with healthy controls, together with reductions in bacteria gene protein expression related to nutrient and energy metabolism, intracellular traffic and defense[62].

HUNGER-SATIETY CIRCUIT: THE ENERGY BALANCE SYSTEM

Hunger and appetite stimulate feeding, although they may not be directly associated with each other. Hunger, an essential part of the instinct of survival, is the physical sensation that triggers eating to refuel the body (calorie input)[44], whereas appetite is the desire for food. Satiety is the end result, the state of feeling full to the point of satisfaction after food consumption.

The hypothalamic hunger-satiety neurocircuitry system, in coordination with external cues, regulates body fat stores by balancing energy intake and energy expenditure over time[44,63]. Systemic hunger-satiety signals include ghrelin, peptide YY, leptin, and insulin. Ghrelin and peptide YY are gut hormones that communicate to the brain the absence/presence of food in the GI tract. Leptin is an anorectic hormone secreted by white adipose tissue[64], and promotes satiety and increasing energy expenditure[65]. Insulin is a hormone secreted by the pancreas that participates in glucose homeostasis[66] and has a similar action as leptin[44].

Figure 2 shows the hunger-satiety circuit. It is essentially comprised of two sets of neuronal subpopulations situated in the arcuate nucleus. The agouti-related protein (AgRP) neurons co-expressing orexigenic AgRP and neuropeptide Y (NPY) stimulate eating and lower energy expenditure. Additionally, adjacent to the AgRP neurons are the anorective cells that co-express pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART). These neurons release α-melanocyte stimulating hormone (α-MSH), which suppresses hunger and increases energy expenditure by binding to the melanocortin-4-receptor (MC4R)[67].

In the fasting state, feeding is stimulated by the binding of ghrelin to the growth hormone secretagogue receptor[68] in the AgRP/NPY neurons. AgRP is then liberated, which antagonizes the binding of α-MSH to the MC4R. In contrast, to end the act of eating, satiety is induced by the binding of the peptide YY, insulin, and leptin to their respective receptors. These actions block the orexigenic effect of the NPY/AgRP neurons and activate the satiety effect of α-MSH[68].

People with excess weight have altered energy balances. Furthermore, they tend more often to make unhealthy food choices compared to those with a healthy weight. It has been documented that the intake of energy-dense food produces a high neuronal reward and stimulation of the dopaminergic BRS pathways, bypassing the physiological regulation of hunger and satiety, especially in subjects that are driven to intake food in response to emotional stimuli[69]. These emotional eaters will repeat this behavior to re-experience this pleasure, which eventually leads to overeating behaviors[70,71]. People with either emotional or cognition alterations can thus develop addictive behaviors, such as low self-control, and low self-efficacy[72,73]. For these people, the small, short-term reward from indulgent foods is more powerful than the long-term benefit of eating healthier food choices.

BRAIN REWARD SYSTEM: THE PLEASURE CENTER

The BRS controls emotions, behavior, learning and

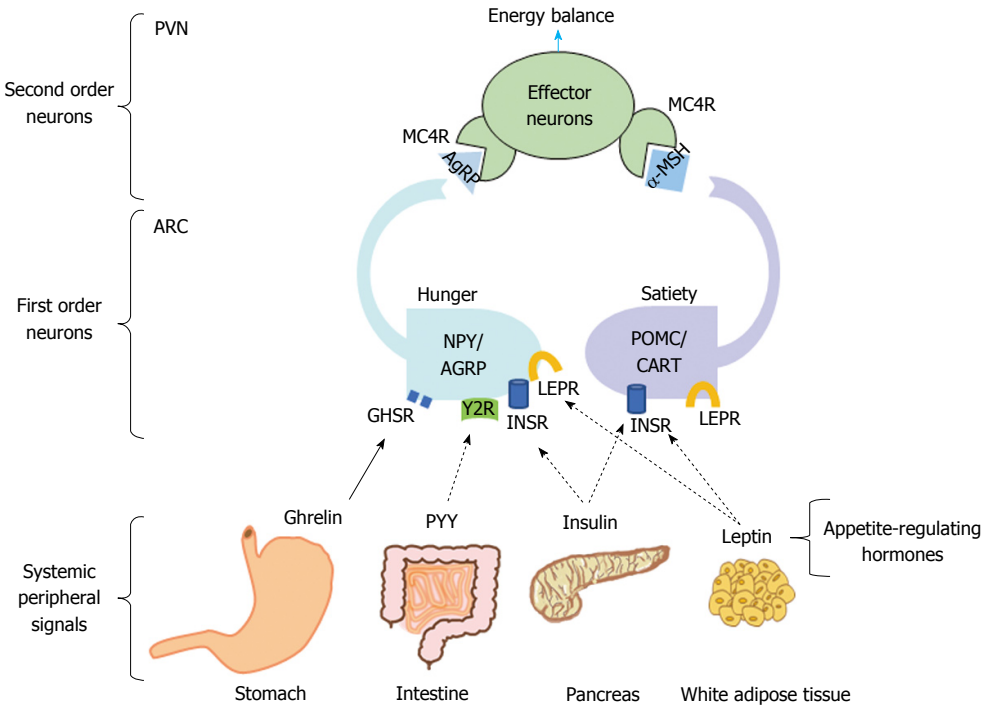

Figure 2 Hunger-satiety circuit and energy balance. Energy balance depends on the appropriate compensatory signals from the hypothalamic nucleus. Food intake is promoted by the binding of ghrelin to the GHSR in the NPY/AgRP neurons, blocking anorexigenic signaling. Once food consumption occurs, PYY-Y2R binding has an antagonistic effect on the orexigenic pathway. Leptin and insulin bind to their specific receptors in POMC/CART neurons that in turn induces α-MSH to bind to its MC4R, promoting satiety. Furthermore, leptin and insulin in NYP/AGRP neurons inhibit AgRP signaling. GHSR: Growth hormone secretagogue receptor; NPY/AgRP: Neuropeptide Y/Agouti-related receptor protein; PYY: Peptide YY; Y2R: Y2 receptor; POMC/CART: Pro-opiomelanocortin/cocaine and amphetamine regulated transcript; α-MSH: α-melanocyte-stimulating hormone; PVN: Paraventricular nucleus; ARC: Arcuate nucleus.

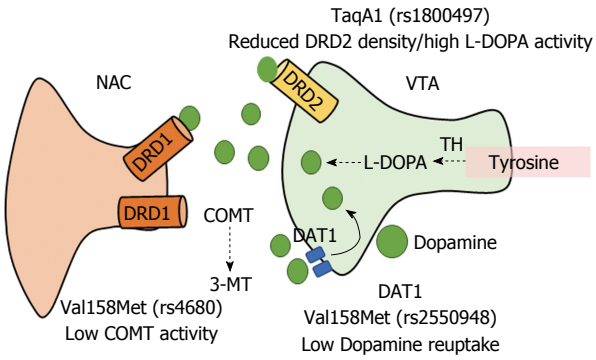

Figure 3 Brain reward dopaminergic signaling between ventral tegmental area and nucleus accumbens neurons. Dopamine in the VTA area activates excitatory DRD1 in the NAC. Several genetic polymorphisms in the regulatory proteins DRD2, DAT1, and COMT modify the reward response to dopamine. VTA: Ventral tegmental area; NAC: Nucleus accumbens; DRD1: Dopamine receptor 1; DRD2: Dopamine receptor 2; DAT1: Dopamine transporter 1; COMT: Catechol-O-methyl-transferase; TH: Tyrosine hydroxylase.

memory, which impact food patterns[74-76]. Various stimuli such as positive emotions, sex, food, and even drugs activate BRS neurotransmitters resulting in feelings of comfort. Not surprisingly, the BRS is more stimulated by highly energy-dense food than to low-calorie food[77]. The BRS is localized in the mesolimbic region and is comprised of the ventral tegmental area (VTA), nucleus accumbens (NAC), amygdala, prefrontal cortex and hippocampus. The BRS is regulated by dopamine, serotonin, Y-aminobutyric acid and glutamate as well as endogenous opioids[76].

Dopamine is the most important neurotransmitter in the BRS. Dopaminergic neurons project from VTA to the amygdala, NAC, pre-frontal cortex, and hippocampus[78]. Figure 3 illustrates the VTA-NAC dopaminergic pathway of the BRS. After stimulation, dopamine synthesis and release from the VTA neurons activates excitatory dopamine one receptors (DRD1) in the NAC. Dopamine transmission concludes by degradation of dopamine by catechol-O-methyl transferase (COMT) by incorporating methyl groups donated by S-adenosyl methionine. When the stimuli have concluded, the dopamine receptor D2/ankyrin repeat domain and content kinase 1 (DRD2/ANKK1) or protein kinase 2 exerts its inhibitory function. Dopamine transporter 1/Solute Carrier Family 6 (DAT1/SLC6A3) uptakes dopamine from the synaptic cleft[79].

However, structural variations in the genetic basis of the hunger-satiety circuit and the BRS may modify the biological response to stimuli, thus explaining some of the differences in emotions, cognition and behavior among individuals.

GENETIC FACTORS

The unveiling of the sequences of the human genome has led to the discovery of heritable single nucleotide polymorphisms (SNPs) that in some cases can have little to no observable effects, but often

Table 1 Gene polymorphisms of the central energy balance and brain reward system

Gene	Locus	SNP (reference sequence)	Risk allele	Clinical implications	Ref.
Central nervous system genes related to hunger and satiety					
LEP	7q31.3	-2548 G>A, (rs7799039)	G	Deficient anorectic signal	Mammès *et al*[84] Hoffstedt *et al*[85]
LEPR	1p31	668 A>G, Gln223Arg (rs1137101)	G	Obesity, low satiety	Boumaiza *et al*[80] Dougkas *et al*[81] Mizuta *et al*[83]
MC4R	18q22	-188 kb T>C, (rs17782313)	C	High energy intake Low satiety	Loos *et al*[88] Acosta *et al*[90]
Brain reward system genes related to emotional disturbances					
DRD2/ANKK1	11q23.2	2137 G>A, Glu713Lys (rs1800497)	A	Addictions, impulsivity, emotional disturbance	Blum *et al*[94]
DAT 1/SLC6A3	5p15.3	G>A, (rs2550948)	A	Impulsivity, increased food intake	Genro *et al*[96] Fontana *et al*[97]
		G>A, (rs2652511)	A		
		G>A, (rs1048953)	A		
COMT	22q11.21	472 G>A, Val158Met (rs4680)	A (Met)	Impulsivity, cognitive function, anxiety, depression	Egan *et al*[101] Gao *et al*[102]
BDNF	11p13	196 G>A, Val66Met (rs6265)	A (Met)	Learning, depression	Bonaccorso *et al*[104]

DRD2/ANKK1: Dopamine receptor 2/ankyrin repeat domain and containing kinase 1 or protein kinase 2 gene; DAT 1/SLC6A3: Dopamine transporter 1/solute carrier family 6 member 3 gene; COMT: Catechol-O-methyltransferase gene; BDNF: Brain-derived neurotrophic factor gene; LEP: Leptin gene; LEPR: Leptin receptor gene; MC4R: Melanocortin-4-receptor gene.

can significantly affect protein structure (where it leads to amino acid sequence changes) and gene expression. Table 1 summarizes several SNPs seen in the energy-balance system and BRS genes involved in less satiety and obesity as well as emotional and cognitive disturbances[80-83] that may be lead to a dysfunctional gut-brain axis. For example, the -2548 G>A polymorphism in the leptin gene decreases leptin concentrations[84,85], whereas the 688 A>G polymorphism in the leptin receptor (LEPR)[86] reduces the receptor's affinity for leptin[87]. The -188 kb T>C polymorphism of the *MC4R* gene[88,89] has been associated with higher energy consumption of fat and proteins, low postprandial satiety and less feeling of nausea in response to overfeeding[88-90].

Furthermore, BRS signaling genes such as *DRD2/ANKK1, COMT, DAT 1/SLC6A3* and *BDNF* (Brain-derived neurotrophic factor) have been related to Reward Deficiency Syndrome (RDS), which consists of a dopamine-based neuronal sensorial deprivation that affects emotions, cognition, and promotes addictive behaviors[91]. Distinct SNPs have been associated with alterations in the core mechanisms of the dopaminergic VTA-NAC pathway. For example, the *DRD2/ANKK1 TaqA1* (rs1800497) polymorphism affects receptor density while increasing L-DOPA activity[92-94]. Several SNPs in the DAT1 transporter protein gene alter the recapture of dopamine[95], which have been associated with impulsivity and increased food intake[96,97]. A reduced COMT activity in the *Val158Met* polymorphism affects the degradation of dopamine and other catecholamines (epinephrine, norepinephrine) causing higher dopamine synaptic levels[98,99]. Stein *et al*[100] have proposed that *Met/Met* carriers be identified as "worriers" whereas the *Val/Val* carriers were known as "warriors" in response to stress resistance. Furthermore, it is thought that obesity behaviors could be related to the *Met/Met* genotype[101-102]. Additionally, the *Val66Met* polymorphism reduces BDNF expression and activity[103], which has been related to obsessive-compulsive disorder, eating disorders, hyperactivity and, attention deficit hyperactive disorder[104]. In fact, Met carriers are more susceptible to depression and anxiety after being exposed to stressful events[105].

GENES-EMOTIONS-GUT MICROBIOTA INTERACTION: REGAINING HEALTH AND HAPPINESS

People with addictions have difficulty in halting the experience of the pleasure reward system, regardless of whether this excessiveness is causing serious damage to the body. Alcohol, tobacco, and a wide variety of drugs are pleasurable stimuli that induce well-being, which of course when consumed in large quantities and over a prolonged period of time, lead to chronic diseases such as alcoholic cirrhosis, lung cancer, or drug abuse. In ancient times, stimulants such as alcohol, peyote, coca leaves and ayahuasca were used by a limited number of people, mainly native priests or shamans, in different religious rites to achieve an altered state of consciousness, while most people did not have free access to them. However, once these were tasted and enjoyed by the rest of the society, the risk of overconsumption leading to addiction became eminent. Nonetheless, these substances are not vital for life, in a biological sense, whereas food is essential for survival. How is it then that the innate need of eating, a pleasure promoted by

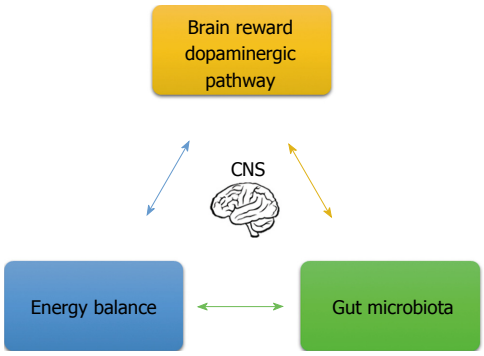

Figure 4 Signals involved in the health/disease process. Brain dopaminergic pathway and energy balance regulate emotional eating behaviors. Negative emotion contributes to alterations in gut microbiota composition. At the same time, gut microbiota environment and its metabolites communicate to the central to the brain and regulate the brain's reward system and energy balance. CNS: Central nervous system.

hunger and appetite ends up as an addiction affecting the GI tract? As explained before, an altered genes-emotions-gut microbiota interaction may be involved. However, social factors should also be considered.

Naturally, a healthy body will respond to the hunger-satiety/reward cycle. However, several decades ago, the global obesity epidemic was not a public health problem. On the contrary, famines and poverty limited access to food and industrially processed food was uncommon, and malnutrition and GI infectious diseases were the mainstream health issues worldwide. Currently, macroeconomic changes resulting from globalization challenge today's societies with a wide variety of foods and flavors, food abundance and 24-h accessibility that promotes overeating. Unfortunately, despite this relative food "wealth", poor people still suffer from hunger, eating cheap, energy-dense foods that cause malnutrition (excess weight), particularly in developing countries.

On the other hand, why people overeat and overload the hunger-satiety/reward system may also be attributable to the genetics of taste preferences. Human taste genes have evolved to distinguish "good" and "bad" tastes, and these genes are highly polymorphic. Additionally, differencing safe food from poisoned (bitter) or damaged food (sour), and to detect sweet or fat tastes in natural/endemic foodstuffs related to energy molecules is a matter of survival[106]. Furthermore, the BRS depends highly on dopamine receptors to elicit the hedonic phase of many human actions, including feeding. What we choose to eat is not based on what is "good" nutritionwise. Instead, our food decision-making depends on the liking of the "good" taste. People who have non-taster alleles for sensing sweets and fats, and have an altered BRS prefer energy-dense foods. Therefore, in an obesogenic environment, these individuals may be at risk for addiction to certain food flavors.

From a metabolic perspective, other genes involved in carbohydrate and lipid metabolism also present risk alleles. Consequently, individuals with these risk alleles consuming an obesogenic diet may develop dyslipidemia, metabolic syndrome and chronic diseases. As the shown in Figure 4, this natural physiological need, as modulated by the brain's energy balance/reward system, makes us seek pleasure. However, by eating the wrong food and feeling negative emotions, this same system may eventually lead to obesity and changes in the gut microbiota starting a vicious cycle. As mentioned before, negative emotions lead to taking refuge in excessively pleasurable stimuli, altering the intestinal microbiota and generating a chronic inflammatory state. The bottom line is that it seems that we no longer enjoy drinking a fine wine, smoking a good tobacco or having a delicious meal in moderation to fulfill the joy of celebration. Instead, this excessiveness has led to addiction, obesity and chronic diseases.

So what is required to regain a healthy genes-emotions-gut microbiota interaction? Based on an integrative genomic medical and nutritional approach, we can state:

Eat ecologically

Globalization, climate changes, and acculturation are only a few of the major threats that have disrupted our relationship with Mother Nature. Human populations that have shifted their regional and traditional ways of life, including their food culture, towards a Westernized lifestyle typical of the "developed world" have lost their ancestral gene-food-culture interconnection, thus leading to higher rates of illness and death due to non-transmissible diseases.

For example, most populations in Latin America countries, such as Mexico are an admixture of Amerindian, Caucasian and African lineages with a rich and traditional food culture. Recent studies in the Mexican population have revealed a higher prevalence of risk alleles of sweet (TAS1R2)[107], fat (CD36)[108,109] and bitter (TAS2R38)[110] taste receptors, lipid-transporting proteins (APO e2 and e4, FABP2)[111], lactose intolerance (LCT-13910 C>T)[112] and neurotransmitter transporters (DRD2 Taq1)[113]. These alleles have been associated with metabolic abnormalities, obesity and alcohol abuse disorders, aggravated by the consumption of a hepatopathogenic and obesogenic diet[114]. Implementation of a genome-based nutritional strategy has been our recommendation to combat these bad eating habits to restore health. The rationale of this strategy is to select foods that balance our inheritance of polymorphic nutrient-interacting genes with the regional ecosystem while preserving the traditional food culture[115].

Enjoy life and be healthy

As the Good Book cites: "The only worthwhile thing for a human being is to eat, drink, and enjoy life's goodness that he finds in what he accomplishes. This,

I observed, is also from the hand of God himself" (Ecclesiastes 2:24). In regards to this point, the BRS allow us to feel pleasure as the natural response to the intrinsic rewards of human life. In other words, we should enjoy eating, drinking and working but without stress, depression, and anxiety. In contrast, extrinsic rewards such as money, are conditioned rewards[116] that may cause in many people who live only for money to have mental and body illnesses more than happiness.

CONCLUSION

In summary, nourishment is a natural and physiological need to obtain energy and seek food from the environment. The brain-gut axis comprises a neural-neuroendocrine circuit between the brain's hunger-satiety and dopaminergic reward systems in conjunction with the gut microbiota, which regulates our emotions and food-decision making. However, genetic variations and the consumption of high-sugar and high-fat diets have overridden this energy/pleasure circuitry to the point of addiction to several foodstuffs as well as obesity and other associated chronic co-morbidities. Balancing this altered physiological process to regain health may involve personalized-medicine and genome-based strategies. Thus, an integrated approach based on the understanding of the genes, emotions and gut microbiota interactions is the next frontier that awaits the gastroenterologist to prevent and treat GI disorders associated with obesity and negative emotions.

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