Review Article

Stress-Related Weight Gain: Mechanisms Involving Feeding Behavior, Metabolism, Gut Microbiota and Inflammation

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Abstract

The body stress response is a highly adaptive phenomenon activated by different types of physical and emotional stressors. Chronic and/or excessive stress is, on the other hand, often maladaptive. In this short review we deal with the influence of the stress response on weight gain and fat accumulation. Chronic stress appears to promote a shift from homeostatic regulation of food intake to hedonic overeating. Hyperactivation of the stress response triggers metabolic changes that might slow down energy expenditure while promoting visceral fat accumulation. Chronically elevated glucocorticoid levels also enhance the inflammatory response and cytokines secreted by visceral fat can in turn increase metabolic abnormalities towards obesity. Changes in the gut microbiota, which is highly sensitive to the stress hormones as well as to the type of food ingested, can also be involved in stress-related weight gain. Given the vicious circles that interlock stress, food, metabolism and inflammation, strategies for stress control and management should be taken into account to prevent weight gain particularly in Western-lifestyle countries.

Keywords: Stress; Weight gain; Food intake; Metabolism; Microbiota; Inflammation

Abbreviations

ACC: Nucleus Accumbens; ACTH: Adrenocorticotropic Hormone; AgRP: Agouti-related Peptide; AMP: Adenosine Monophosphate; ARC: Arcuate Nucleus; AVP: Arginine Vasopressin; BAT: Brown Adipose Tissue; CART: Cocaine- and Amphetamine- Regulated Transcript; CRH: Corticotropin Releasing Hormone; GCs: Glucocorticoids; GLP-1: Glucagon-like Peptide-1; GR: Glucocorticoid Receptor; HPA: Hypothalamo-Pituitary-Adrenal Axis; HSL: Hormone-Sensitive Lipase; IL-6: Interleukin-6; LPL: Lipoprotein Lipase; LPS: Lipopolysaccharides; MCP-1: Macrophage Chemoattractant Protein-1; MDR: Multidrug Resistance; α-MSH: α-Melanocyte Stimulating Hormone; NPY: Neuropeptide Y; POMC: Pro-Opiomelanocortin; PVN: Paraventricular Nucleus; SCFAs: Short Chain Fatty Acids; TNF-α: Tumor Necrosis Factor-α; TRH: Thyrotropin Releasing Hormone; UCP-1: Uncoupling Protein-1; VTA: Ventral Tegmental Area; WAT: White Adipose Tissue.

Introduction

We eat to live. Our body requires constant energy for the maintenance of life processes, but the intake of food is discontinuous by its nature, so a complex system of regulation, using signals of hunger and satiation, connects "belly" and "brain" to control energy homeostasis and the maintenance of a constant body weight [1].

We also eat for pleasure. The hedonic aspect of food does not apply to homeostatic energy balance, but involves other brain areas including those assigned to emotions, cognitive functions and the circuitry of pleasure and reward [2].

An alteration in appetite during periods of stress is a common experience for human beings. Actually, the systems that control food intake and the stress response relate anatomically and functionally and converge at the level of the hypothalamus, so that both systems can affect each other in determining a behavioral response [3].

Moreover, the stress hormones, namely adrenaline and cortisol, have profound effects on body metabolism, driving to hyperglycemia, insulin and leptin resistance and, ultimately, obesity and metabolic syndrome [4,5].

A growing body of evidence indicates the gut microbiota as a "microbial organ" associated to the gastrointestinal tract, capable of performing different functions, among which there are regulation of body metabolism and capacity to extract energy from nutrients, modulation of inflammation and immunity and shaping of the stress response [6].

In this short review we deal with the influence of the stress response on eating behaviors and food choice, on the regulation of body metabolism, on the gut microbiota and on the inflammatory response. All these evidences point to chronic stress as a major risk factor for the prevalence of obesity in Western-lifestyle countries.

Overview of the stress response

The body stress response is an adaptive response to environmental challenges, either physical or emotional. The individual stress response is stereotypical and involves the activation of the nervous system as well as of endocrine signals [7]. The nervous axis involves activation of the locus coeruleus/sympathetic nervous system and the release of catecholamines from the adrenal medulla into the blood stream. This is the "fight or flight response" originally described by Walter Cannon

[8]. Catecholamines secreted from the adrenal medulla and sympathetic nerves drive the rapid mobilization of body energy from storage sites to heart, muscle and brain. Increased cardiovascular activity, blood pressure and breathing rate allow the transport of glucose, nutrients and oxygen to target tissues. At the same time, the stressor acts on the paraventricular nucleus (PVN) of the hypothalamus and stimulates the release of CRH and AVP into the hypophysial portal circulation. CRH is the first hormone of the endocrine axis that regulate the activity of the adrenal cortex, that is the hypothalamo-pituitary-adrenal (HPA) axis [9]. Hypothalamic CRH and AVP stimulate the corticotrope cells of the anterior pituitary to release ACTH, which in turn acts on the adrenal cortex to stimulate glucocorticoids (GCs) secretion. Cortisol is the main GC in humans (while corticosterone is in rodents): it supports metabolism during the stress response mainly by stimulating gluconeogenesis in the liver and lipolysis in the adipose tissue, so that the body has available fuel to face the stressors. Moreover, GCs act a negative feedback to prevent further HPA axis activation. Triggering of the stress system increases arousal, motor reflexes, attention, cognitive function and tolerance of pain, but it decreases cell and body growth, reproductive and digestive functions, and has a profound impact on immunomodulation [7,9].

The stress response is highly adaptive in acute states, when it is rapidly activated and inactivated bringing back the organism to its basal homeostasis. This is the concept of "good" stress, termed "eustress" since the studies of Selye that generally refers to a stress response of limited time duration. Chronic activation of the stress response is, on the other hand, often maladaptive and referred to as "distress" [10]. According to the theory of allostasis, carried out by Sterling and Eyre [11], the organism faces chronic stress by accumulating allostatic load in the attempt to adapt to the environmental challenges. When, on an individual basis settled by personal stress resilience, the allostatic load is too heavy, the organism faces the "wear and tear" of the regulatory systems, resulting in biological alterations and metabolic impairment that weaken adaptive processes and increase susceptibility to diseases [12].

Overview of the regulation of food intake: homeostatic and hedonic mechanisms

The regulation of food intake in humans is complex and mainly regulated by the so-called "homeostatic" and "hedonic" mechanisms.

The homeostatic control of food intake is essential to preserve the body energy balance and homeostasis, leading to the maintenance of a constant body weight throughout life. This is achieved through the action of different peripheral signals the connect belly and brain, informing about the presence of nutrients in the gut, blood and liver. Along with these "short-term" satiation signals, "long-term" signals originate in the body periphery to inform about energy status and adiposity [13].

The brainstem, particularly the dorsal vagal complex, is the principal central site receiving short-term satiation signals traveling through the vagus nerve, such as volumetric information on gastric distension. At the same time, the enteroendocrine cells in the intestinal mucosa, sensitive to the chemical properties of nutrients, secrete a multitude of hormonal mediators of satiation including cholecystokinin, GLP-1, oxyntomodulin, peptide YY, pancreatic polypeptide and others. The stomach also produces ghrelin, a unique hunger signal, which levels are inversely proportional to gastric distension [14].

While gut peptides modulate food intake on a short-term basis, circulating levels of insulin from the endocrine pancreas and leptin, secreted by adipocytes, are proportional to adipose tissue amount and involved in the long-term regulation of energy balance [1].

The hypothalamus, specifically the arcuate nucleus (ARC), ultimately receives and integrates the great majority of peripheral short- and long-term signals of hunger and satiety. Within the ARC, there are two neuronal populations, the so-called primary neurons, with opposite effects on food intake: the orexigenic neurons co-express NPY and AgRP and stimulate food intake; the anorexigenic neurons co-express POMC (from which the melanocortin α-MSH is derived) and CART, which inhibits appetite. The primary neurons project to second-order neurons, also located in the hypothalamus, e.g., in the PVN and in the lateral area. Here other orexigenic (e.g., orexins) and anorexigenic (e.g., CRH and TRH, that also affect metabolic rate) are produced and the modulation of this complex network eventually determines the proper eating behavior to maintain homeostasis [15].

Despite the homeostatic mechanism described above, when food consumption is gratifying for us, we are driven to eat regardless of our energy balance. The food, particularly if highly palatable, high-fat and high-sugar stimulates the dopaminergic system of reward, the same implicated in alcohol and drugs abuse and addiction. The reward circuitry includes the ventral tegmental area (VTA), the nucleus accumbens (ACC), the dorsal striatum, and also overlaps with limbic areas (amygdala, cingulate, hippocampus, insula) related to emotions [2].

Negative emotions favor hedonic consumption of fats and sugars, while if we are happy we are satisfied even by less appetizing foods [16]. The pleasure linked to the reward is attributed to the activity of opioid neuropeptides of the mesolimbic system, while at the level of the lateral dorsal striatum, an alteration of endocannabinoids results in the implementation of automatic and repetitive actions, including eating habits. Moreover, the prefrontal cortex is involved in the modulation of cognitive behavioral instincts, adjusting impulses, cravings, desires [17,18].

It is increasingly clear that the appetite mediators not only have a role in the homeostatic regulation of eating behavior, but also in the hedonic one (cognitive, emotional, reward-related) [19,20].

Orexins for example, that are secreted by hypothalamic second-order neurons, activate the dopaminergic neurons of the VTA [21]. Insulin and leptin, that signal satiety at the ARC, also inhibit the reward circuitry [22]. A recent paper shows evidence that the differential regulation in the rewarding value of sugars and lipids is due to a galanin-mediated inhibitory actions of leptin on orexin neurons [23]. On the contrary, ghrelin activates the reward circuitry and drives to food consumption even already satiated rats [24].

Stress and eating behaviors

It appears clear that the homeostatic control of food intake and the stress system share the same anatomy and converge at the PVN of the hypothalamus. Thus the link between stress and eating behaviors is unbreakable [3,25,26]. The destabilizing aspect is that both in animals and in humans, facing with stressors might either increase or decrease food intake. This is partially due to the opposing effects on food intake exerted by the two main hormones of the HPA axis, i.e., CRH and GCs.

By its nature, the stress response suppresses appetite: when homeostasis is threatened, the sense of hunger, the search for food and

the digestive activity (motility, secretion and absorption) are inhibited, because not a priority. The stress hormones, adrenaline and cortisol, help to enhance blood glucose levels and under acute stress cortisol stimulates the secretion of insulin. High levels of glucose and insulin in the blood are a satiety signal. In addition, CRH (and other CRH-like peptides, such as urocotin) exhibits a direct anorexigenic activity, since it is able to act at the ARC, where it inhibits the activity of NPY/AgRP neurons [27].

On the other hand, GCs stimulate appetite. First, cortisol operates a negative feedback control on the secretion of CRH, thus relieving the anorexigenic signal. It also acts directly on the ARC by stimulating the expression of NPY and AgRP via AMP-activated protein kinase signaling [28]. In addition, high levels of cortisol increase the production of ghrelin, which stimulates hunger [29].

The action of GCs overwhelms that of CRH at the end of the acute stress event. Cortisol has a longer half-life in blood with respect to CRH, and exerts long-term effects via the interaction with specific intracellular receptors (GRs). This is appropriate to recover the energy spent to face the stressors, according to a perfect homeostatic mechanism.

However, in case of chronic stress or if there are multiple sequential stressors, GC levels can be maintained chronically elevated, leading to increase feeding and consequently to obesity [4].

Studies on animal models show that rats exposed to chronic stress increase their food intake if they have access to "confortable" high-calorie foods [30]. Actually, GCs particularly stimulate the appetite for high palatable and high-calorie food. Confortable food and cortisol together directly activate the dopamine reward circuitry and the high levels of dopamine contribute to extinguish, as part of a negative feedback regulation, the activity of the HPA axis [18].

Moreover, while promoting the release of leptin from the adipose tissue, GCs contribute to leptin resistance, because they decrease the sensitivity of the hypothalamus to the hormone, thus reducing the satiating action. Leptin also inhibits the ACC; therefore, a vicious circle arises leading to a constant increase in the intake of "comfortable" food to maintain the pleasure/reward effect [31]. As in the case of leptin, GCs also stimulate insulin secretion from the pancreas, which normally reduces both food intake and the reward circuitry. However, chronically elevated GC levels contribute to insulin resistance [32].

It was observed that in humans chronic stress causes an increase in food consumption in approximately 40% of subjects, but a decrease in another 40%, while 20% of individuals do not alter their feeding behavior [33,34]. These varying results may relate not only to the type of stressor (physical, mental, emotional, social) and its duration, but mainly to personality traits, the emotional relationship with food and personal resilience [3,33]. In this regard, research efforts of the past decades indicate that pre- and peri-natal stressful experiences, either physical or psychological, and hostile environmental factors exert long-term consequences on health via altered epigenetic regulation. An increased risk of obesity and an increase in food intake were detected in adults and children undergoing pre- and peri-natal stress such as malnutrition, separation from parents, physical and psychological abuse. Thus, stress biology may represent an underlying mechanism mediating the effects of diverse intrauterine perturbations on brain and peripheral targets of programming of body composition, energy balance homeostasis and metabolic function [5,35-37].

Stress and metabolism

The shift towards the hedonic overeating caused by stress can be functional in acute situations, but it is not in the long run. GCs exert a complex action on the regulation of lipid homeostasis, affecting both the turnover and uptake of fatty acids in adipose tissue [38]. In the acute stress response, GCs enhance lipolysis through the activation of hormone-sensitive lipase (HSL) [39]. Nevertheless, it has been shown that they also stimulate the activity of adipose lipoprotein lipase (LPL), which promotes fat storage [40]. LPL activity, GR expression and 11β-hydroxysteroid dehydrogenase 1 (the enzyme that converts inactive GC metabolites in active GCs) activity are greater in visceral fat than in other adipose depots. Moreover, GCs, together with insulin, play a critical role in the proliferation and differentiation of adipocytes. Taken together, all these observations point to the association between elevated GC levels and visceral fat accumulation [4].

Besides the effects on white adipose tissue (WAT), it should be mentioned that GCs are among the strongest down-regulators of UCP-1 expression in brown adipose tissue (BAT), thus contributing to a reduction in thermogenesis and a conservation of energy that could, in a chronic setting, promote obesity [41].

Prolonged activation of the stress system leads to decreased synthesis of thyroid hormones due to increased concentrations of CRH-induced somatostatin, which in turn suppresses the hypothalamo-pituitary-thyroid axis. Furthermore, elevated circulating GCs inhibit the conversion of inactive thyroxine to the biologically active triiodothyronine in peripheral target tissues [42]. Thyroid hormones are well known for their pivotal role in regulating body metabolism, resting metabolic rate and energy homeostasis [43]. The lipolytic effects of thyroid hormones in adipose and non-adipose tissues are also widely known. More recently, the thyroid hormone derivative 3,5-diiodothyronine (T2) has been shown to activate lipid-lowering mechanisms in target tissues [44,45]. Therefore, the inhibition of thyroid function by GCs may represent another mechanism linking chronic stress, dysmetabolism and obesity.

Stress and gut microbiota

Within the gut there are ten times more micro-organisms than the number of cells in the human body. This "microbial organ" performs important functions for the host, such as nutrient harvesting and immune development [46].

It is well known that stress and HPA activation can influence the composition of the gut microbiota. For example, repeated social stressors have been shown to decrease the relative abundance of Bacteroides while increasing that of Clostridium. This effect appears to be mediated by the production of inflammatory cytokines [47].

The relationship between the stress response and the gut microbiota is bidirectional. Psychological stress can also increase gut permeability [48-50], allowing bacteria and antigens to cross the epithelium and activate a mucosal immune response. Cytokines produced by activated immune cells can in turn enhance the activation of the HPA axis. Prevention of gut leakiness by intestinal microbiota modulation by probiotcs leads to attenuated HPA response in rats [51].

Increasing evidence points to a role of commensal organisms in early programming and later responsiveness of the stress system [52]. Animals raised in a germ-free environment show an exacerbated HPA activation upon psychological (restraint) stress, which is ameliorated by probiotic treatment, but in a time-dependent manner [53,54]. This

means that early gut colonization is necessary for the normal development and activity of the stress response.

In a recent review the mechanisms by which the gut microbiota can alter eating behaviors are summarized and discussed. Suggested mechanisms comprise modulation of pain signaling, modulation of taste receptor expression, neural mechanisms, production of hormone analogs and neurochemicals [55]. Numerous commensal and pathogenic bacteria manufacture peptides that are strikingly similar to hormonal mediators of satiety and hunger, such as leptin, ghrelin, peptide YY, NPY [56].

Diet plays a major role in determining the composition of gut microbiota: Prevotella grows best on carbohydrates; dietary fiber provides a competitive advantage to Bifidobacteria, and Bacteroidetes has a substrate preference for certain fats [57,58]. In obese individuals, it has been shown an alteration of the microflora composition, which is often characterized by the prevalence of Firmicutes with respect to Bacterioidetes. This could contribute towards the development of obesity, mainly through the effects of LPS on promoting inflammation and the role of SCFAs which are produced as bacterial metabolites of dietary compounds [59].

Taking together all these evidences, it appears that a vicious circle can arise linking stress, food choice, dysbiosis and obesity.

Stress and inflammation

Inflammation is indeed recognized nowadays as the common base of most chronic ad metabolic disease, including metabolic syndrome and obesity, typical of developed Western-lifestyle countries [60].

Catecholamines acting on β-adrenergic receptor exposed on immune cells stimulate the proinflammatory immune response in a predictive manner that is functional to protect the organism while coping with stressors. The subsequent action of GCs is to dump down the inflammatory response to protect the body from excessive inflammation and bring the organism back to homeostasis at the end of the stress response [61]. On the other hand, the parasympathetic nervous system prevents excessive inflammation by activation of reflexes through afferent and efferent fibers of the vagus nerve [62].

It has been demonstrated that cytokines released by activated immune cells are able to act on the hypothalamus and trigger the HPA axis and that cortisol, in turn, suppresses the proinflammatory response as part of a negative feedback regulation [63].

However, chronic stress response activation is often accompanied by an increase in the proinflammatory response rather than a decrease. This is likely due to cortisol resistance, which occurs when immune cells become less sensitive to the anti-inflammatory effects of GCs in order to compensate for their continuous secretion [64]. Different mechanisms underlying GC resistance have been proposed and documented, including modulation of GC availability (e.g., by influencing corticosteroid binding globulin, the multidrug resistance (MDR) P-glycoprotein transporter and 11beta-hydroxysteroid dehydrogenase activity) as well as GR dysfunction due to reduced expression, binding affinity to its ligand, nuclear translocation, DNA binding, or interaction with other transcription factors [65].

Moreover the increase in visceral fat stimulated by cortisol during chronic stress provides a potential link between systemic inflammation and abdominal obesity. Excessive visceral (mesenteric and omental) fat could cause metabolic abnormalities by secreting inflammatory

adipokines, such as IL-6, TNF-α, MCP-1, and resistin, which induce insulin resistance and diabetes [66-68].

Conclusions

The body stress response is a highly adaptive stereotypical response that enables the organism to prepare for, respond to and cope with physical and emotional stress. However, chronic and/or excessive stress causes cumulative negative impacts on health. The body accumulates "allostatic load" just in the attempt to adapt to continuous environmental challenges and maintain allostasis.
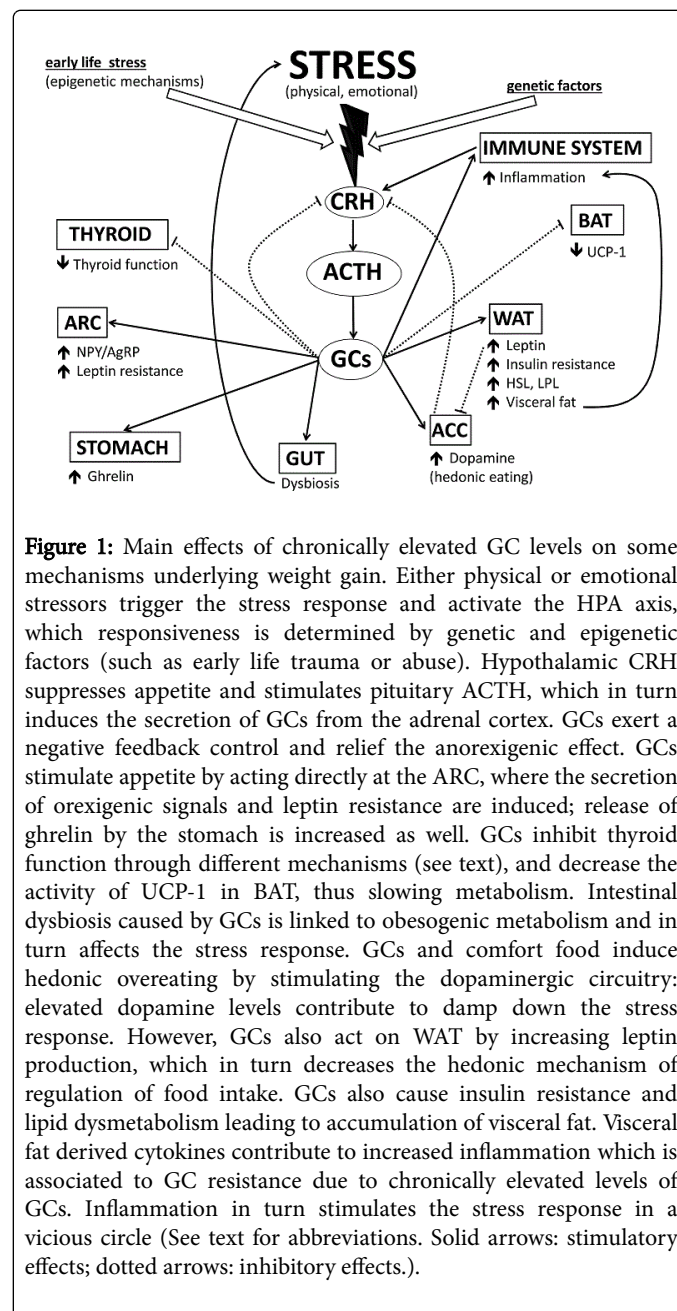

Figure 1: Main effects of chronically elevated GC levels on some mechanisms underlying weight gain. Either physical or emotional stressors trigger the stress response and activate the HPA axis, which responsiveness is determined by genetic and epigenetic factors (such as early life trauma or abuse). Hypothalamic CRH suppresses appetite and stimulates pituitary ACTH, which in turn induces the secretion of GCs from the adrenal cortex. GCs exert a negative feedback control and relief the anorexigenic effect. GCs stimulate appetite by acting directly at the ARC, where the secretion of orexigenic signals and leptin resistance are induced; release of ghrelin by the stomach is increased as well. GCs inhibit thyroid function through different mechanisms (see text), and decrease the activity of UCP-1 in BAT, thus slowing metabolism. Intestinal dysbiosis caused by GCs is linked to obesogenic metabolism and in turn affects the stress response. GCs and comfort food induce hedonic overeating by stimulating the dopaminergic circuitry: elevated dopamine levels contribute to damp down the stress response. However, GCs also act on WAT by increasing leptin production, which in turn decreases the hedonic mechanism of regulation of food intake. GCs also cause insulin resistance and lipid dysmetabolism leading to accumulation of visceral fat. Visceral fat derived cytokines contribute to increased inflammation which is associated to GC resistance due to chronically elevated levels of GCs. Inflammation in turn stimulates the stress response in a vicious circle (See text for abbreviations. Solid arrows: stimulatory effects; dotted arrows: inhibitory effects.).

Figure 1 summarizes the main effects of chronically elevated GC levels on some mechanisms underlying weight gain. With regards to eating behaviors, chronic stress appears to promote a shift from

homeostatic to hedonic regulation of food intake. Actually, hedonic overeating acts as a mechanism of relief of stress symptoms, but, on a long-time basis, this behavior can lead to obesity. Moreover, hyperactivation of the stress response triggers metabolic changes that might slow down energy expenditure while promoting visceral fat accumulation. Enhanced inflammatory response due to chronically elevated GC levels and cytokines secreted by visceral fat can in turn increase metabolic abnormalities towards obesity and non-communicable diseases. Stress-related weight gain can also be sustained by changes in the gut microbiota, which is highly sensitive to the stress hormones as well as to the type of food ingested.

In Western-lifestyle countries, high stress levels, lack of sleep, pollutants and endocrine disruptors, the abundance of cheap, highly palatable, energy-dense foods, the inadequate balance between physical activity and mental effort contribute to shaping the so-called "obesogenic environment", that imposes many difficulties in maintaining a constant body weight [69-71]. Keeping in view the functioning of the stress system and the theory of allostasis, fat gain can be perceived as an allostatic response of the organism trying to achieve a physiological compensation to unhealthy lifestyle. Given the vicious circles that interlock stress, food, metabolism and inflammation, strategies for stress control and management appear to be a first line of defense against obesity and Western-lifestyle non-communicable diseases.

Acknowledgements

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