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Review

Metabolic consequences of stress during childhood and adolescence

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ABSTRACT

Stress, that is, the state of threatened or perceived as threatened homeostasis, is associated with activation of the stress system, mainly comprised by the hypothalamic-pituitary-adrenal axis and the arousal/sympathetic nervous systems. The stress system normally functions in a circadian manner and interacts with other systems to regulate a variety of behavioral, endocrine, metabolic, immune, and cardiovascular functions. However, the experience of acute intense physical or emotional stress, as well as of chronic stress, may lead to the development of or may exacerbate several psychologic and somatic conditions, including anxiety disorders, depression, obesity, and the metabolic syndrome. In chronically stressed individuals, both behavioral and neuroendocrine mechanisms promote obesity and metabolic abnormalities: unhealthy lifestyles in conjunction with dysregulation of the stress system and increased secretion of cortisol, catecholamines, and interleukin-6, with concurrently elevated insulin concentrations, lead to development of central obesity, insulin resistance, and the metabolic syndrome. Fetal life, childhood, and adolescence are particularly vulnerable periods of life to the effects of intense acute or chronic stress. Similarly, these life stages are crucial for the later development of behavioral, metabolic, and immune abnormalities. Developing brain structures and functions related to stress regulation, such as the amygdala, the hippocampus, and the mesocorticolimbic system, are more vulnerable to the effects of stress compared with mature structures in adults. Moreover, chronic alterations in cortisol secretion in children may affect the timing of puberty, final stature, and body composition, as well as cause early-onset obesity, metabolic syndrome, and type 2 diabetes mellitus. The understanding of stress mechanisms leading to metabolic abnormalities in early life may lead to more effective prevention and intervention strategies of obesity-related health problems.

1. Introduction

Childhood and adolescence are periods of continuous physical growth and emotional development, and great brain plasticity. Strong evidence has suggested that the experience of intense acute or chronic stress during these critical periods of life may have long-term and frequently irreversible effects on emotion; behavior; growth; metabolism; and reproductive, immune, and

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cardiovascular function [1,2]. Both lifestyle and neuroendocrine mechanisms contribute to the development of metabolic and other alterations in stressed individuals [3]. Typically, but not necessarily, an obese phenotype mediates the effects of chronic stress on metabolism. This article summarizes the mechanisms and the effects of stress during fetal life, childhood, and adolescence, with emphasis on metabolic consequences. It provides also a review of the existing pediatric literature on the effects of physical and emotional stress in these crucial periods of human development.

1.1. *Mechanisms of stress*

Stress, the state of threatened or perceived as threatened homeostasis, is associated with activation of the stress system, which is located in the central nervous system and the periphery of the organism. The stress system consists mainly of 2 axes, the hypothalamic corticotropin-releasing hormone (CRH) system, regulating the hypothalamic-pituitary-adrenal (HPA) axis and the brainstem locus caeruleus/norepinephrine (LC/NE) system, regulating arousal and autonomic (sympathetic) nervous system function [4-6]. Centrally, the main mediators of the stress system are the hypothalamic paraventricular nucleus hormones CRH and arginine vasopressin, the arcuate nucleus proopiomelanocortin-derived peptides α-melanocyte–stimulating hormone and β-endorphin, and the brainstem NE produced in the A1/A2 centers of the LC and the central nuclei of the sympathetic nervous system (SNS). In the periphery, the end-effectors of the HPA axis are the glucocorticoids; and those of the sympathetic system are the catecholamines epinephrine and NE [4-6]. In addition to the main components and mediators of the stress system, other systems and their mediators, which can be neurotransmitters, hormones, cytokines, and growth factors, interact with them to further regulate and fine-tune homeostasis. The targets of all these stress and related mediators are brain structures with functions related to emotion and behavior, as well as central nervous system and peripheral tissues related to growth, metabolism, reproduction, immunity, and cardiovascular function.

In normal conditions, activation of the stress system caused by everyday stressors results in adaptive endocrine, metabolic, and cardiovascular changes that help maintain homeostasis [7]. However, the experience of intense real or perceived stressors, such as accidents, natural disasters, war or terrorism, physical or sexual abuse, bereavement, etc, can lead to excessive and prolonged activation of the stress system or, in a subgroup of individuals, to chronic hypoactivation of this system, with a variety of psychologic and biological consequences [4-7].

Chronic hypersecretion of stress hormones, as evidenced by elevated cortisol and catecholamine concentrations in the circulation, results in insulin hypersecretion and growth and sex steroid hormone hyposecretion. These effects lead to long-term accumulation of fat especially in visceral adipose tissue, loss of muscle (sarcopenia), and osteoporosis with adverse clinical and metabolic consequences, including arterial hypertension, carbohydrate intolerance, dyslipidemia (metabolic syndrome), and type 2 diabetes mellitus [4,5,8,9].

Glucocorticoids, secreted by the adrenal cortices, together with the autonomic nervous system, play a crucial role in the stress response, altering target tissue activities and shifting metabolism toward catabolism [9-13]. Circulating cortisol in humans has a circadian pattern of secretion regulated by the suprachiasmatic nucleus of the hypothalamus [14]. The zenith of cortisol concentrations is reached in the early morning; and the nadir, at midnight. Recent data have shown that the circadian rhythm transcription factor Clock acetylates the glucocorticoid receptor (GR) and represses GR-induced transcriptional activity of several glucocorticoid-responsive genes [15]. Clock and its heterodimer partner brain muscle ARNT-like protein 1 play an essential role in the formation of the circadian rhythm of central and peripheral systems. Furthermore, the peripheral Clock regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man [16]. The effects of this system on the sensitivity of target tissues to cortisol suggest that even mild dysregulation of stress system activity, such as the chronic slight evening elevations of cortisol associated with chronic stress, in conjunction with the elevated evening sensitivity to glucocorticoids, may explain the development of central obesity and consequent metabolic alterations in chronically stressed individuals [14-17].

2. Stress, circadian rhythms, and adipokines

During stress, the end-effectors of the HPA-axis, the glucocorticoids, stimulate appetite [18] and increase body weight through the orexigenic effect of the hypothalamic feeding signal neuropeptide Y [19], an effect that is inhibited by leptin and insulin [20]. During the last 2 decades, the adipose tissue–derived hormone leptin has emerged as an important regulator of energy homeostasis, as well as a regulator of reward processing, brain development, neuroendocrine and immune function, and metabolism [21,22]. Leptin interacts with the HPA axis [23], whereas an inverse relation has been found between rapid fluctuations in circulating leptin concentrations and corticotropin and cortisol in healthy men [23]. The metabolic effects of this hormone result from coordinate activation of anorexigenic and inhibition of orexigenic pathways, mediated by leptin-responsive neurons in the hypothalamus [24].

In accordance to circulating cortisol, leptin concentrations follow a circadian rhythm, with highest values between midnight and early morning and lowest in the early to midafternoon [21]. This circadian rhythm of leptin may be affected by sleep loss, as evidenced by a study in healthy men in sustained sleeplessness [25]. This study revealed that the diurnal amplitude of leptin is reduced during sleep deprivation and returns toward normal during the period of recovery sleep [25]. Furthermore, it has been shown that sleep and fasting condition result in additional systematic decreases in leptin, glucose, and insulin, whereas wakefulness and food intake result in a systematic increase in leptin concentrations [26]. More recent data examining the effects of misalignment between behavioral cycles of sleep/wake and fasting/feeding and circadian cycles revealed adverse metabolic and cardiovascular consequences and, more specifically, decreased leptin, increased insulin and glucose, and a completely reversed cortisol rhythm [27]. Moreover, the human circadian system seems to modulate a variety of cardiovascular risk markers (autonomic, hemodynamic, and hemostatic) with consequent profiles that might contribute to the higher distribution of adverse cardiovascular events through the day/night circles [28]. These studies imply that sleep/wake patterns, which are frequently disturbed during stressful situations [29], are important regulators of the daily ranges of circulating leptin, which by influencing food intake and energy balance may contribute to the development of obesity in stressed individuals [30].

Decreased sleep is also associated with increased risk for obesity-related complications, such as diabetes and hypertension [30-34]. The combined effects of stress pathophysiology together with the behavioral/circadian misalignment might provide a mechanism underlying the increased risk for obesity, hypertension, and diabetes in chronically stressed individuals with disturbed sleep/wake patterns [3,5,27-34].

Fewer evidence exists on relations between stress, behavior, and the adipose tissue–derived protein, adiponectin, whereas these associations are, in most cases, mediated by obesity or obesity-related metabolic complications [30,35]. Adiponectin is decreased in obesity [36], whereas hypoadiponectinemia is related to adverse metabolic and cardiovascular outcomes in humans [36-41]. Recent data have shown that high–molecular weight adiponectin also has a significant day/night rhythm that is not driven by the feeding/fasting cycle. However it is not well known whether the diurnal rhythm of high–molecular weight adiponectin interacts with the daily rhythms of insulin sensitivity [42].

3. Why stress is more damaging during childhood

There is solid evidence that factors acting during fetal life, childhood, and adolescence have a substantial effect on health and well-being of the individual throughout the life span [43,44]. In addition to early life indicators, such as gestational age, birthweight, early growth patterns, and onset of puberty, individual differences in behavioral and physiological adaptation during stressful situations may play important roles in mediating early life factors to coronary heart disease, type 2 diabetes mellitus, stroke, depression, and cognitive functioning in adulthood [45]. Fetal life, childhood, and adolescence are periods of incessant physical growth and brain development. Although the concepts of stress adaptation have been developed with reference to adults, the same principles also apply to children and adolescents. Chronic alterations in the activity of the stress system, expressed either as hyper- or hypofunctioning of the HPA axis and the LC/NE-SNS, during these periods of life may have permanent effects on brain development and endocrine and metabolic systems (Fig. 1) [1-3,44,46,47]. Endocrine systems, which are crucial for growth and puberty, including the gonadal, growth hormone, and thyroid axes, are influenced by the HPA axis. These axes are inhibited at several levels by stress mediators, whereas estradiol and thyroid hormones stimulate the stress system [2-5]. Timing of puberty and final stature may be influenced by chronic hypersecretion of stress mediators.

The experience of chronic and/or severe stress in adults may result in some sensitization of mature brain structures, whereas there is evidence that such alterations of biological stress systems may have permanent effects in chronically stressed children [44,46,47]: Studies in animals have shown that elevated levels of cortisol and catecholamines may lead to alterations in brain development through mechanisms of accelerated loss of neurons [48], delays in myelination [49], or abnormalities in developmentally appropriate pruning [50]. Elevated levels of glucocorticoids during intense stress may also result in frontal lobe deficiencies, amygdala hyperfunctioning, hippocampal damage, and consequent learning and

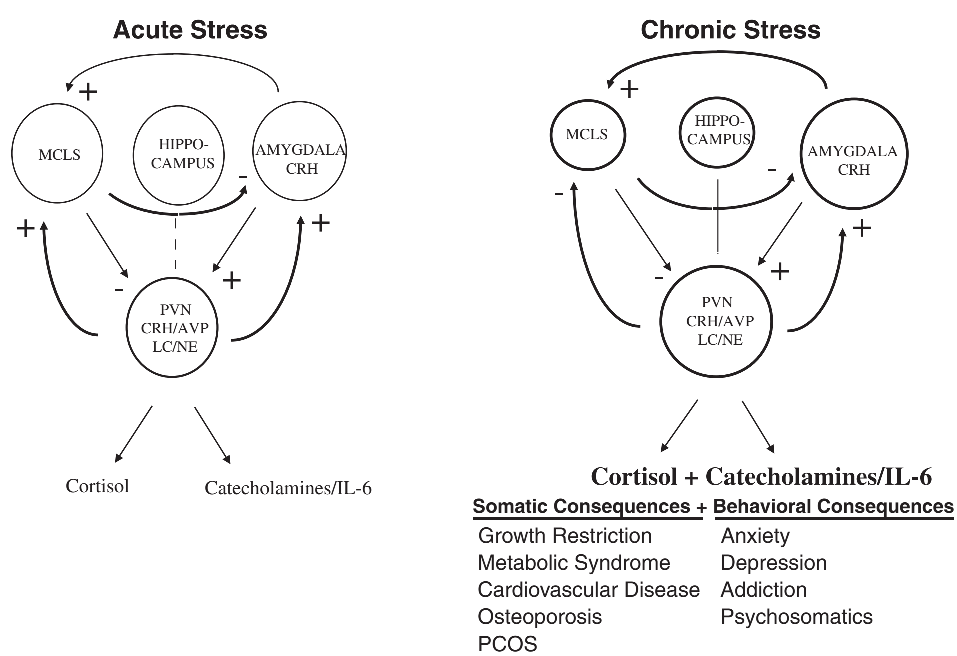

Fig. 1 – Acute and chronic stress and potential consequences. Adapted from Chrousos and Gold [46]. MCLS indicates mesocorticolimbic (reward) system; PVN, paraventricular nucleus; AVP, arginine vasopressin.

concentration difficulties [51]. Fluctuations of stress mediators during periods of brain plasticity may permanently "program" the brain to be vulnerable to stress. Such alterations in brain structures and functions may contribute to the development of behaviors related to food intake and reward.

4. Effects of physical stress

Severe injuries, burns, sepsis, and surgical or critically ill situations lead to significant cardiometabolic alterations, characterized by a hyperdynamic circulatory response associated with increased body temperature, glycolysis, lipolysis, and proteolysis [52]. Physical stress has also been shown to produce a variety of metabolic abnormalities in children; however, the contribution of concurrent emotional stress is not always clear or measurable. Pediatric burn patients provide an example of stress-related metabolic dysfunction, even after the acute phase: Insulin sensitivity was measured in a study of severely burned children before discharge, when wounds were 95% healed, with a 2-hour oral glucose tolerance test. The homeostasis model assessment of insulin resistance index was significantly higher in burned children compared with values in healthy children [53]. A variety of cellular stress-signaling pathways are thought to be activated as a result of the burns. Another study in pediatric burn patients revealed that stress-induced insulin resistance persisted not only after the acute phase but for up to 3 years postburn [54]. Several stress mediators, such as urinary cortisol, epinephrine, NE, serum interleukin (IL)-7, IL-10, IL-12, macrophage inflammatory protein-1b, monocyte chemoattractant protein–1, and resting energy requirements were significantly increased in this group of 194 children for up to 36 months postburn. Serum insulin and C-peptide remained also significantly increased for the entire period of 36 months, whereas serum glucose was high for 6 month postburn. It is quite likely that insulin resistance is due to the marked increases in endogenous stress hormones and inflammatory stress mediators [54].

Sepsis represents another physical stressor with potential metabolic complications. Children with meningococcal disease often show hyperglycemia on admission. A study in critically ill children with meningococcal infection showed that both insulin resistance and β-cell dysfunction play a role in the occurrence of hyperglycemia in these children [55]. The effects of physical injury on stress hormones and adipocytokines were examined prospectively in children and adolescents after motor vehicle accidents [56]. Stress hormones were compared longitudinally between a group with physical injury and a group of children that experienced only emotional stress associated with a traffic accident. In the aftermath of the trauma, serum cortisol was higher in the physically injured group, whereas IL-6 concentrations were increased in both trauma groups compared with controls, indicating that both physical and psychological stress produce similar elevations of this cytokine. In the same study, adiponectin was lower in the physically stressed group than the emotionally stressed and the control groups; and this was mainly attributed to females. Circulating catecholamines and leptin did not differ between groups. Serum cortisol and IL-6 normalized 1 month after the accident and remained normal 6 months later. Adiponectin in the physically injured group, in females, remained low 1 and 6 months after the accident, indicating a persistent effect of physical stress on this adipocytokine, which may represent a potential risk factor for further development of cardiovascular disease [56].

5. Effects of emotional stress

Epidemiologic studies link anxiety disorders and depression to adverse health outcomes, such as type 2 diabetes mellitus and cardiovascular disease in adults [57,58], whereas obesity and obesity-related metabolic abnormalities possibly mediate such relations. In fact, anxiety and depression have been linked to abdominal obesity, elevated blood pressure, and metabolic abnormalities, such as insulin resistance and an abnormal lipid profile [59]. Further to stress-related psychopathology, the experience of intense and/or chronic stress, especially during childhood, may also produce clinical and metabolic abnormalities related to adverse health outcomes.

5.1. *Anxiety disorders and depression*

Both behavioral and biologic pathways mediate relations between anxiety/depression and metabolic abnormalities in adults and children (Fig. 2). There is evidence that anxiety and mood disorders are related to dysregulation of the HPA axis, as evidenced by centrally elevated CRH concentrations and/or increased or decreased peripheral cortisol concentrations in serum, urine, or saliva and increased, in most cases, catecholamines in urine or plasma [60-62]. Pediatric patients with a history of exposure to chronic stress and/or suffering from anxiety, posttraumatic stress disorder (PTSD), or depression have, in most cases, high peripheral cortisol concentrations, especially in the evening [63-65]. Similarly, increased catecholamine concentrations are noted in most cases, as evidenced by high epinephrine and NE levels in urine and plasma [63-65].

One of the first neuroendocrine studies in sexually abused girls with depression and suicidal behavior revealed significantly greater 24-hour urinary concentrations of catecholamines and their metabolites than matched controls [66]. The same group of children exhibited reduced evening, CRH-stimulated, plasma corticotropin concentrations compared with matched nonabused, symptom-free girls [67]. Longitudinal data in children and adolescents with PTSD after accidents [63] revealed that the group that developed and maintained PTSD, an anxiety disorder that develops after traumatic life events, manifested a longitudinal divergence of the 2 axes of the stress system, with NE increasing and cortisol gradually decreasing over time. These neuroendocrine changes reflect a potential mechanism of how chronic stress can lead to chronic hormonal disturbances with potential clinical and metabolic consequences.

Limited studies have investigated directly the role of peripheral cortisol in mediating the chronic effects of stress on obesity. A study in adults revealed that patients with depression and urinary cortisol levels in the highest tertile had an increased prevalence of the metabolic syndrome, which suggests that hypercortisolemic depression constitutes a specific risk factor for the metabolic syndrome [68]. Because

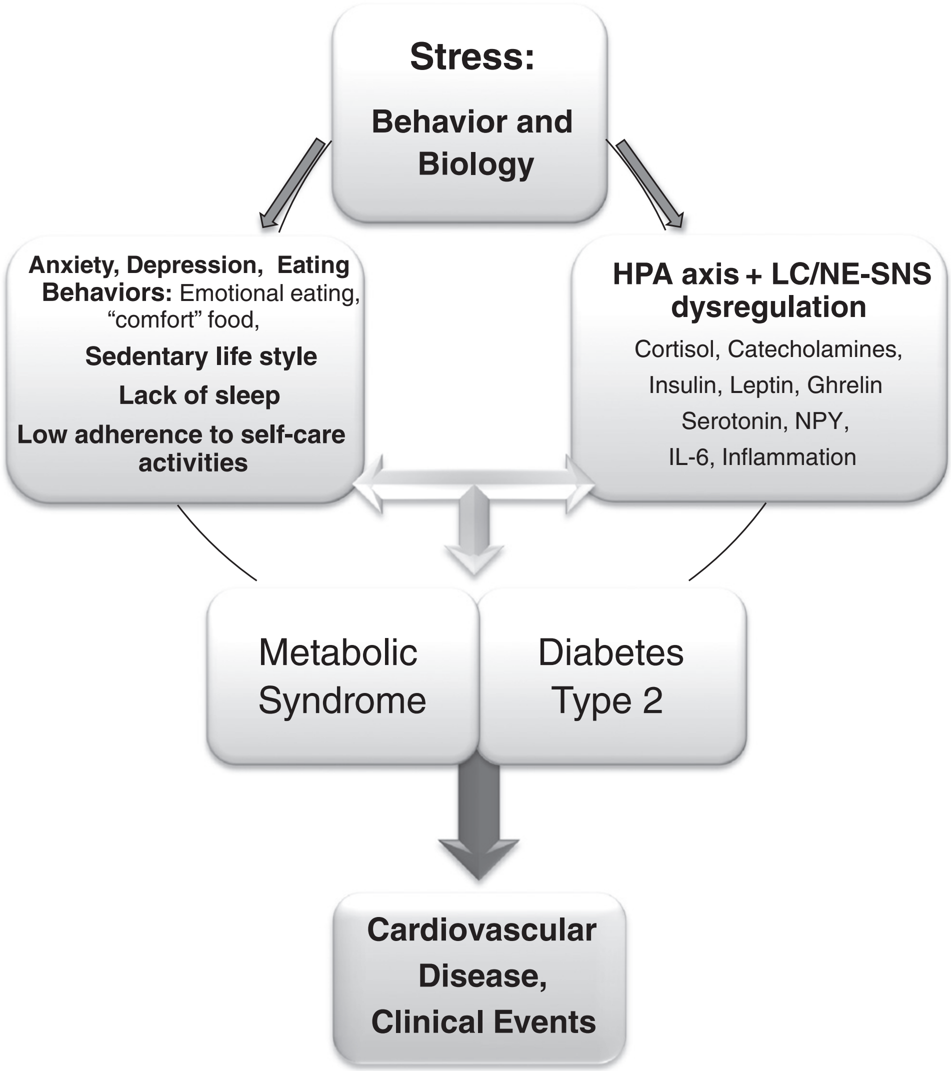

Fig. 2 – Biologic and behavioral pathways linking stress to obesity and the metabolic syndrome.

metabolic syndrome cannot be diagnosed in childhood and most often develops later in life, studies linking directly anxiety disorders/depression, HPA dysregulation, and metabolic syndrome in childhood are lacking.

In addition to cortisol and the catecholamines, other molecules also link stress and obesity/metabolic abnormalities: glucocorticoids induce insulin and leptin secretion, and cause the "leptin resistance" that characterizes obesity. Stress-induced cortisol abnormalities are also followed by elevated neuropeptide Y secretion and disruption of food intake regulation. Recent data also support that insulin and leptin play important roles in the regulation of central pathways related to food reward [69].

In addition to dysregulation of the HPA axis and LC/NE-SNS in chronically stressed individuals, disturbed eating behaviors and lifestyle parameters also contribute to the development of metabolic abnormalities (Fig. 2). Stress-related eating behaviors, such as emotional eating and consumption of "comfort" foods [70], are of great importance in the pathogenesis of obesity. In fact, a study in overweight children and adolescents showed that increased anxiety was associated with emotional eating and loss of control over eating. It was found that emotional eating mediated the relation between anxiety and loss of control, whereas depression in the same group was associated with emotional eating as well [70]. The researchers assumed that the emotional eating behavior is a way of coping with anxiety and hyperarousal because children feel that it provides distraction and comfort from painful negative emotions. Furthermore, children suffering from chronic stress are typically characterized by poor adherence to self-care activities and sedentary habits, such as exaggerated television viewing and Internet use. These sedentary habits correlate with obesity, especially in adolescent girls, independently of the level of physical activity [71].

Sleep disturbances is a common feature of chronic stress in children. A variety of cross-sectional epidemiologic studies in adults and children have shown that sleep duration is inversely associated with obesity, whereas prospective studies have found that a short sleep duration predicts weight gain or obesity over the follow-up period. Furthermore, sleep deprivation was shown to predict type 2 diabetes mellitus in adults [72]. Recent studies have shown that hormones that regulate glucose homeostasis and appetite are influenced by sleep. Sleep problems and disorders, such as difficulties in sleep onset, duration, and quality, are some of the most prevalent symptoms in pediatric stress-related disorders. Sleep susceptibility is in general modulated by the interaction of the central nervous system circadian rhythmicity and sleep-wake homeostasis. During sleep, glucose levels remain stable, despite prolonged fasting, in contrast to a decrease in fasting conditions in the waking state [73].

5.2. *Childhood stress and trauma*

The experience of intense stress or trauma during childhood may also produce adverse adult health outcomes: a retrospective study in adults who survived the siege of Leningrad in 1941-1944 when they were children, adolescents, or young adults revealed that women who were 6 to 8 years old and men who were 9 to 15 years old at the peak of the starvation period had higher systolic blood pressure than unexposed individuals. Furthermore, higher mortality from ischemic heart and cerebrovascular disease was noted in women and men exposed at ages 6 to 8 and 9 to 15, respectively, showing that the experience of severe physical and emotional stress in childhood may have long-term consequences in survivors [74].

Research has also shown that the experience or childhood adversity may lead to the development of obesity and associated morbidity: a prospective study revealed that female victims of childhood abuse, in comparison to their nonabused peers, were more likely to manifest obesity in early adulthood and show high-risk growth trajectories throughout development [75]. Furthermore, neuroendocrine studies have shown that the experience of childhood abuse may disrupt the neurobiology of the HPA axis and LC/NE-SNS, providing support for the hypothesis of attenuation of cortisol across development, that is, cortisol hyposecretion subsequent to cortisol hypersecretion [65,76].

5.3. *The example of anorexia nervosa*

Anorexia nervosa is a condition of severe undernutrition, initiated in most cases during adolescence and characterized by alterations in multiple neuroendocrine axes and peptides that regulate energy intake [77]. This condition of chronic stress is associated with dysregulation of the HPA axis [5,77], as expressed by hypercortisolemia together with low insulin-like growth factor 1 (IGF-1), triiodothyronine (T3), insulin, and leptin concentrations and increased ghrelin and peptide YY concentrations [77-81]. Both chronic stress and severe undernutrition contribute to the metabolic changes found in individuals with anorexia nervosa; however, high cortisol and peptide YY concentrations seem to be associated with psychopathology (disordered eating) independent of body mass in women across the spectrum of body mass index [82].

Although the majority of alterations related to undernutrition are adaptive to low caloric intake and body weight, they affect body composition, puberty, final stature, bone metabolism, and reproduction [83,84]. Recent promising data have shown that leptin administration in replacement doses in women with hypothalamic amenorrhea may be a safe and effective therapy correcting the abnormalities in the gonadal, thyroid, growth hormone, and adrenal axes, as well as in markers of bone metabolism [85,86].

6. Fetal stress and programming of the adipose tissue

The fetal origins of adult disease hypothesis, which originated from the epidemiologic research of Barker and colleagues, demonstrated an association between low birth weight and hypertension, insulin resistance, dyslipidemia, and cardiovascular disease later in life [87]. The researchers, in an attempt to explain this association, proposed the "thrifty" phenotype hypothesis, according to which the fetus in a poor intrauterine environment maximizes the uptake and conservation of fuel resources by altering its metabolism. This alteration is adaptive in a deprived environment but maladaptive in an environment of plentiful resources [88]. The hypothesis of predictive adaptive response, however, expands the one suggested by Barker and colleagues beyond energy use and conservation. According to predictive adaptive response, developmentally plastic processes are used to set a postnatal physiological and behavioral phenotype that the stressed fetus predicts in an attempt to ensure an optimal chance for survival. The prediction of a deprived and hence stressful environment leads to adaptive changes in body size, organ size, body composition, neuroendocrine activity, and behavior. These predictive adjustments that could be advantageous in a stressful environment are maladaptive in conditions of plenty [88,89].

Both human and animal studies have shown that early nutritional stress, as expressed by exposure of the fetus and infant to inadequate or excessive amounts of nutrition, is associated with an increased risk for obesity, metabolic syndrome, and type 2 diabetes mellitus in later life. A main concept of the fetal origins of adult disease hypothesis supports that prenatal exposure to excessive or deficient nutrition alters the development of the adipocyte (adipogenesis). These alterations consist of a permanent increase in the capacity to form new cells in the adipose tissue and/or to store lipids in existing adipocytes (lipogenesis) [90,91]. Adipogenesis occurs mainly during late fetal and early postnatal life and is a highly sensitive process to the nutritional environment at this time frame. The number of adipocytes is relatively fixed in adulthood, with a very low turnover rate of adipose cells, supporting further the idea that fetal and early postnatal periods are crucial for the development of adipose tissue.

Growth-restricted humans or animals in fetal life have lower adipose stores at birth. However, the postnatal exposure to a nutrient-rich environment results in growth acceleration (catch-up) and increased visceral adipose tissue accumulation. Apart from fetal growth restriction, maternal obesity and maternal gestational diabetes constitute further risk factors for childhood obesity and related disease. Based on animal data, it has been hypothesized that changes in gene expression within visceral adipocytes before birth influence the subsequent properties of subcutaneous adipose tissue that continues to develop. These "programmed" adipocytes may secrete factors that promote preadipocyte differentiation in other depots, resulting in further increase in adipocyte number [91].

Recent data have also revealed an association between prenatal stress and subsequent shorter telomere length in young adulthood, which is a predictor of age-related disease onset and mortality, expanding the existing literature of the effects of fetal stress on health and disease [92].

7. Conclusions and perspectives for future research

In conclusion, today, there is strong evidence that physical and emotional stress during critical periods of growth and development has permanent effects on body size and composition, tempo of growth and sexual maturation, metabolism, and behavior, resulting in adverse health outcomes in later life. However, although stress is often implicated in the pathogenesis of a host of diseases and, more specifically, the development of obesity and/or metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease, it is not easy to estimate its quantitative contribution at this time. The nature and the chronicity of the stressor, as well as the vulnerability to and perception of stress by the individual, are important variables in determining the chronic adverse effects of stress. Furthermore, the metabolic effects of stress and their cardiovascular sequelae result from both dysregulation of stress hormone secretion and unhealthy lifestyle-related behaviors, such as excessive and/or deficient nutrition, chronic lack of sleep, irregular life routines, and a sedentary life [93].

The inclusion of stress as a variable in the estimation of metabolic and cardiovascular risk, even from the early stages of human development, would be an important contribution to the determination of high-risk groups for further morbidity and mortality. In this effort, both assessment instruments related to real or perceived stress, as well as biological markers, such as circulating stress hormones and cytokines, might be necessary to calculate such risk. The recognition of stress as a variable determining health-related risks might lead to improved methods for prevention and intervention and the development of family-, group-, and individual-based strategies to reduce stress and its damaging consequences in high-risk populations.

Conflict of Interest

The authors have nothing to declare. There is no conflict of Interest. None of the authors have relevant financial interests in this manuscript, and we certify that no financial support has been given for this work.

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