Paediatric stress: from neuroendocrinology to contemporary disorders

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ABSTRACT

Background Stress is defined as a state of threatened or perceived as threatened homeostasis. A broad spectrum of extrinsic or intrinsic, real or perceived stressful stimuli, called ‘stressors’, activates a highly conserved system, the ‘stress system’, which adjusts homeostasis through central and peripheral neuroendocrine responses. Inadequate, excessive or prolonged adaptive responses to stress may underlie the pathogenesis of several disease states prevalent in modern societies. The development and severity of these conditions primarily depend on the genetic vulnerability of the individual, the exposure to adverse environmental factors and the timing of the stressful event(s), given that prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors.

Materials and methods We conducted a systematic review of original articles and reviews published in MEDLINE from 1975 through June 2016. The search terms were ‘childhood stress’, ‘pediatric stress’, ‘stress and disorders’ and ‘stress management’.

Results In this review, we discuss the historical and neuroendocrine aspects of stress, and we present representative examples of paediatric stress system disorders, such as early-life adversity, obesity and bullying. We also discuss the adverse impact of a socio-economic crisis on childhood health. The tremendous progress of epigenetics has enabled us to have a deeper understanding of the molecular mechanisms underlying paediatric stress-related disorders.

Conclusions The need for early successful stress management techniques to decrease the incidence of paediatric stress-related diseases, as well as to prevent the development of several pathologic conditions in adolescence and adulthood, is imperative.

Keywords Childhood adversity, childhood bullying, childhood obesity, paediatric stress, stress, stress management.

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Historical aspects of stress

The concepts of stress have their origins in ancient Greece [1–3]. Pythagoras, a pre-Socratic philosopher, used the term harmony to refer to the equilibrium of the universe (The harmony of the Cosmos). This balance was achieved by the concurrent activity of numerous disturbing and counteracting forces and was later termed isonomia by Alcmaeon of Croton [1,3]. Empedocles of Argigentum proposed that the harmony of the universe is established when the four basic elements (=rhizomata or racins), namely earth, water, air and fire, achieve a balance. Hippocrates of Cos, the father of medicine, was the first to use the term health to describe the harmonious balance of the four humours: blood, phlegm, black and yellow bile, which correspond to the heart, the brain, the liver and the spleen, respectively [1,4]. According to the Hippocratic humoral system, eucrasia was defined as the balance of the four humours, whereas dyscrasia described their imbalance. Both eucrasia and dyscrasia originate from nature; therefore, ‘Nature is the healer of diseases’. According to Epicurus, the mind could be a healer of human disease. Therefore, ataraxia or ‘imperturbability of mind’, and aporia (lack of pain) represent the most desirable states [1,3].
During Renaissance, Thomas Sydenham suggested that an adaptive response to any stressful stimuli leading to an individual’s systemic disharmony could cause pathologic changes [5]. Many years later, Claude Bernard underlined the fundamental role of an internal medium, the *milieu intérieur*, which surrounds cells while providing a steady state. An important historical milestone of stress concepts was the work of Walter Bradford Cannon, who was the first to use the term homeostasis (from the Greek *homoios*, or similar, and *stasis*, or position) to describe the physiologic processes that contribute to the balance of the organism. Walter Bradford Cannon also suggested the concept of fight or flight reaction to describe an animal’s reaction to threatening conditions [1,5]. Indeed, the adaptive response to stressors triggers the activation of arousal and the sympathetic nervous system and leads to increased secretion of catecholamines, thereby priming the animal for fight against the threat or fleeing to save its life.

In the 20th century, Hans Hugo Bruno Selye, a pioneer Hungarian endocrinologist, borrowed the term stress from physics and described it as a ‘nonspecific neuroendocrine response of the body’ [6]. Selye was the first to introduce the term General Adaptation or Stress Syndrome describing the presence of common clinical manifestations often observed in severely ill patients due to prolonged adaptation responses. Moreover, he coined the term heterostasis (from the Greek *heteros*, or other, and *stasis*, or position) to refer to ‘stability through change’ [1,3]. Selye also believed that different states of stressful conditions could cause different effects on human health; therefore, eustress consisted of all those states of stress that could enhance human growth and development at the emotional and intellectual level, whereas distress represented those stressful conditions that could cause unpleasant feelings and severe pathologic conditions [1,3]. In addition to introducing novel concepts related to stress, Selye contributed significantly to the field of neuroendocrinology of the stress response, suggesting a pivotal role of the adrenal cortex-derived ‘corticoids’ in the maintenance of basal and stress-related homeostasis. Furthermore, his pioneering studies convincingly demonstrated that glucocorticoids, a term that he introduced, exert strong anti-inflammatory effects [7].

**Neuroendocrinologic organization of the stress system**

The stress system consists of the hypothalamic–pituitary–adrenal (HPA) axis and the locus caeruleus (arousal)/norepinephrine–autonomic nervous systems, which crosstalk and have multiple sites of interaction with other systems [1,3,8] (Fig. 1). Indeed, the stress system interacts with the mesocortical and mesolimbic dopaminergic reward system, the central nucleus of the amygdala, which participates in the generation of fear and/or anger, as well as with the hippocampus, the central organ of memory. Moreover, the activity of the stress system is influenced by fundamental neurochemical modulators, such as serotonin, acetylcholine and γ-aminobutyric acid (GABA). Finally, molecules, such as neuropeptide (NP) Y, leptin and substance P, contribute to the regulation of stress system activity [1,3,8].

The HPA axis consists of the paraventricular nuclei (PVN) located in the hypothalamus, the pituitary gland and the adrenal cortices. Upon activation by a broad spectrum of stressors above a certain threshold, neurons of the PVN produce and release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophysial portal system. CRH and, to a lesser degree, AVP trigger the synthesis and secretion of ACTH by the anterior pituitary gland. ACTH is derived from pro-opiomelanocortin (POMC), a prohormone that functions as a precursor for several bioactive molecules, such as beta-endorphin- and alpha-melanocyte-stimulating hormone. Importantly, POMC participates in the regulation of the HPA axis activity, granted that the *Pomc* gene in the pituitary gland is downregulated through negative feedback mechanisms of the HPA axis. The secreted ACTH, then, reaches the adrenal cortex through the systematic circulation and induces the production of glucocorticoids [1–3,8,9]. These steroid hormones regulate many functions essential for life, such as growth, behaviour, cognition, reproduction, as well as metabolism, through catabolic actions in the liver, muscle and adipose tissue, and exert potent anti-inflammatory and immunosuppressive effects. All these pleiotropic glucocorticoid actions are mediated by the human glucocorticoid receptor (hGR), an intracellular protein that acts as a ligand-induced transcription factor influencing gene expression in a positive or negative fashion [10].

The locus caeruleus/systemic sympathetic/sympathomedullary and parasympathetic systems regulate many physiologic functions, such as those of the neuroendocrine, cardiovascular, respiratory, renal and gastrointestinal systems. During the ‘fight or flight reaction’, arousal is activated and the sympathetic system induces the secretion of epinephrine and norepinephrine, followed by activation of the HPA axis and secretion of cortisol. In addition to epinephrine, norepinephrine and cortisol, the sympathetic and parasympathetic systems signal through numerous neuropeptides, lipid mediators of inflammation, adenosine triphosphate (ATP) and/or nitric oxide [1,8].

**The adaptive stress response**

During stressful conditions, the stress system is activated through two serial waves of hormonal secretion to adequately achieve homeostasis. The first wave involves the following: (i) increased...
concentrations of catecholamines (epinephrine and norepinephrine) from the locus caeruleus and the sympathetic nervous system; (ii) elevated plasma ACTH concentrations due to increased secretion of hypothalamic CRH; (iii) decreased LH secretion from the anterior pituitary; and (iv) increased release of prolactin (PRL) and growth hormone (GH). The second wave occurs a little later and involves the elevated production and secretion of glucocorticoids, the end products of the HPA axis [11].

The two above-discussed hormonal waves lead to a series of physical and behavioural adaptation changes that ultimately increase the chances of the organism to survive [12]. Indeed, stressed organisms increase their respiratory rate and cardiovascular tone and switch intermediary metabolism into a catabolic state in order to redirect oxygen and nutrients to the central nervous system (CNS) and the stressed body site(s), namely the heart and skeletal muscles, both crucial components of the fight or flight response. Moreover, when organisms have to cope with stressors, they may present with increased arousal, alertness, focused attention, improved cognition, as well as enhanced analgesia, elevated affect, suppression of feeding and inhibition of reproductive function. Concurrently, organisms activate restraining mechanisms to prevent an excessive response of the stress system [1,8,12].

The adaptive stress response is determined by multiple genetic, developmental and environmental factors. Indeed, polymorphisms of genes encoding molecules involved in the stress response, such as CRH, AVP, and their cognate receptors and/or regulators, seem to play an important role in the adaptive response to stressors [8]. Moreover, transitional life stages, such as prenatal life, infancy, childhood and adolescence, are critical periods characterized by increased plasticity of the stress system and, therefore, increased sensitivity to stressors [8,13]. Any prolonged and/or excess actions of the stress hormones exerted on certain target tissues during these developmental stages may reprogramme the stress system and cause detrimental effects in adult life. Finally, the quality of early-life environment seems to strongly influence the stress response through epigenetic alterations occurring in genes of the stress system, including increased methylation of the GR exon variant 1F in humans or the GR 17 in rats [14].

**Paediatric stress system disorders**

The quantity and quality of adaptive stress response must be appropriate to effectively achieve homeostasis. In contrast, improper responsiveness to stressors turns homeostasis to
cacoostasis and increases the vulnerability to the development of acute or chronic pathologic conditions [2,3,8,12]. Nowadays, our modern society is plagued by multifactorial noncommunicable diseases, such as obesity/metabolic syndrome and their detrimental cardiovascular complications. Moreover, the ever-increasing socio-economic crisis appears to increase youth’s exposure to adversity and cause earlier precocious life transitions leading to increased risk for cardiovascular disease in adulthood [15]. Below, we will discuss some representative examples of contemporary paediatric stress system disorders.

**Early-life adversity**

A growing body of evidence suggests that early life plays a fundamental role in the adaptive response to stress. Indeed, early-life adversity alters the activity of HPA axis through epigenetic mechanisms, including DNA methylation [14]. Thirty years ago, Meaney et al. demonstrated that early postnatal maternal handling of rats altered glucocorticoid receptor concentrations in the hippocampus. Interestingly, increased frequency of pup licking/grooming (LG) was associated with increased hippocampal expression of glucocorticoid receptor, which provided a less potent stress response, possibly through a greater negative feedback inhibition of hypothalamic CRH and pituitary ACTH [16]. Subsequent in vivo studies showed that high maternal LG resulted in increased concentrations of thyroid hormone, enhanced serotonin signalling and increased binding of the transcription factor NGFI-A to the 17 promoter of the glucocorticoid receptor gene [17–19]. On the other hand, low maternal LG caused increased hippocampal cytosome methylation of the 17 promoter, an epigenetic modification that resulted in decreased hippocampal expression of the glucocorticoid receptor, ultimately altering the adaptive stress response [19].

Early-life adversity was further studied in humans with consistent results. Individuals who committed suicide and had a history of childhood abuse had increased methylation of the hippocampal hGR gene compared with their counterparts, who did not have a history of abuse or were otherwise healthy [20] (Fig. 2). Several subsequent animal and human studies confirmed that early environmental adverse experiences might reprogramme the HPA axis activity through decreased expression of the glucocorticoid receptor [14]. Interestingly, some of these human studies have shown an increased methylation of the hGR promoter in peripheral leukocytes of individuals who experienced childhood maltreatment, disruption of parent–offspring interactions or childhood parental loss [21–23]. These interesting results demonstrate that epigenetic modifications may occur in different cell populations and point towards broader genomewide analyses. Furthermore, not only the hGR gene, but also other genes encoding molecules participating in the stress response undergo epigenetic modifications.

Indeed, maternal separation for a prolonged period is associated with altered methylation state of the Avp gene, increasing AVP production from the hypothalamus and, therefore, the HPA response to stress [24]. Under similar conditions, the Pomc gene is hypomethylated, an epigenetic phenomenon that results in elevated basal and CRH-induced levels of ACTH [25]. Finally, childhood maltreatment is associated with differential states of methylation of the FKBP5 gene, resulting in increased expression of FKBP5 and decreased glucocorticoid signalling [26].

In contradistinction to childhood maltreatment, early skin-to-skin contact has been shown to attenuate stress reactivity in both mothers and their infants. Several studies demonstrated that skin-to-skin contact decreased cortisol concentrations, therefore buffering the infant’s stress response [27–29]. A recent randomized trial showed that skin-to-skin contact (touch) for an average of 19 h per day during the first week of life reduced salivary cortisol reactivity in preterm infants and their mothers [30]. These results concur with a previously published study by Feldman et al. [29], who showed that maternal skin-to-skin contact had sustained effects in lowering stress reactivity 10 years later.

**Childhood obesity/metabolic syndrome**

Chronic stress and obesity/metabolic syndrome in children are closely inter-related through well-recognized biological and behavioural pathways. Prolonged activation of the stress system results in increased secretion of neuroendocrine mediators, such as cortisol, norepinephrine, epinephrine, immune CRH and interleukin (IL)-6, which contribute to hypersecretion of insulin and decreased release of GH and sex steroids. All these hormonal alterations synergistically cause visceral fat accumulation, loss of muscle mass (sarcopenia) and bone mass (osteopenia/osteoporosis). The resultant visceral obesity associated with insulin resistance and dyslipidemia, in association with hypertension, all represent the cardinal clinical manifestations of the metabolic syndrome and its heightened risk for cardiovascular complications [2,3,13]. In addition to obesity, chronic stress may cause anxiety and/or depressive feelings, which typically result in sedentary habits, emotional eating patterns and increased consumption of comfort foods, as well as in poor adherence to self-care activities [31]. Consequently, these behavioural pathways further increase visceral fat accumulation. On the other hand, obese children often have low self-esteem and feelings of guilt, finally entangling in a vicious cycle of distress and weight gain [32].

In addition to the profound effects of child stress on obesity and vice versa, accumulating evidence suggests an important role of parent and family stress in the multifactorial pathogenesis of stress-related childhood obesity [33]. Indeed, greater levels of parent-perceived stress are associated with increased
child fast-food consumption, ultimately leading to obesity [34]. Furthermore, parents with high levels of stress may have less motivation necessary to engage with their children, which results in increased screen time [35]. Moreover, impaired home and family structure seems to increase the likelihood of becoming obese. Family disruption, housing issues, financial strains and lack of cognitive stimulation and emotional support are among the most common stressors associated with the home environment [36]. Several studies have shown that an impaired family structure is associated with overweight in children either through lack of energy in their parents and/or due to elevated cortisol concentrations in the child or the adolescent [36,37].

Childhood and adolescent bullying

Nowadays, bullying in children and adolescents is a common experience of repeated maltreatment to maintain or improve one’s social hierarchy status [38]. Bullying victims have long-lasting and pleiotropic health consequences, including increased susceptibility to viral illnesses, impaired appetite, abdominal pain and sleep disorders [39]. One of the possible mechanisms linking bullying with adverse mental and physical health functioning could be chronic systemic low-grade inflammation [38]. Indeed, bullied individuals exhibit greater concentrations of C-reactive protein (CRP), a marker of low-grade systemic inflammation, compared with those not involved in bullying. In contrast, bullying of others caused lower concentrations of CRP. The increased concentrations of CRP in victims could be attributed to changes in the activity of the stress system [38]. Victims of chronic bullying have a blunted secretion of cortisol in response to a social stress test, indicating lower exposure to the anti-inflammatory effects of cortisol and higher inflammatory state [40,41].

Childhood bullying has been associated with epigenetic modifications of the HPA axis response to stressors. Ouellet-Morin and coworkers used a discordant monozygotic (MZ) twin design to examine whether bullying altered serotonin transporter gene (SERT) DNA methylation [42]. The study findings indicated that bullied twins had higher methylation state of SERT gene at the age of 10 years than their nonbullied MZ cotwins. Furthermore, victims with higher methylation of SERT gene had blunted cortisol secretion, suggesting a possible functional association of these two systems [42].

Socio-economic crisis and stressful life transitions

Developed societies are increasingly detrimentally impacted by socio-economic inequalities and adversities, characterized by limitations in financial and other resources, as well as greater exposure to social injustices, negligence and marginalization. Of note, negative life events are very common, while community stress is ever increasing. It is now accepted that such stressful circumstances may cause a precocious acquisition of adult roles, which consists of off-time events, such as the birth of children at an earlier age, dropping out of school and/or searching for a job [15]. Studies that investigated the additive influences of family and community adversities on cardiometabolic disease risks of young adults demonstrated that early youth’s exposure to adverse socio-economic events was
significantly associated with a higher risk of increased levels of cardiometabolic biomarkers, such as blood pressure, waist circumference, pulse rate, HDL and HbA1c [15]. These results are likely to strengthen future studies aimed to elucidate the molecular/biological pathogenetic mechanisms linking socio-economic adversity with cardiometabolic diseases and will identify this contemporary stressor as a novel target for stress management intervention.

Future directions: the need for early intervention through stress management techniques

It is now imperative to develop and apply effective stress management methods to decrease the incidence and alleviate the clinical manifestations of paediatric stress system disorders, as well as to prevent the development of any detrimental health consequences in adolescence and adulthood. Although progressive muscle relaxation and diaphragmatic breathing have been effectively applied in several stressful conditions in adulthood [43–55], we still need studies investigating the efficacy of stress management methods in children and adolescents with a history of early-life adversity or bullying, as well as in paediatric populations suffering from obesity/metabolic syndrome or other stress-related disorders. As our lifestyle is particularly permissive for cacostasis, and given that early adverse effects may influence our expressed genome in a negative fashion through epigenetic modifications, prevention strategies are necessary. Therefore, awareness in paediatricians should be increased, stress management methods should be taught in medical schools, and broader stress management programmes should be applied in vulnerable populations, particularly in developed societies. In addition to paediatricians, teachers, school psychologists or other school personnel trained in stress management methods could contribute to decrease distress in children and adolescents. We have recently evaluated the effectiveness of an 8-week stress management programme, which included diaphragmatic breathing, progressive muscle relaxation, guided imagery and cognitive restructuring, in overweight and obese children and adolescents, who followed a Mediterranean (Cretan) diet and were encouraged to adopt lifestyle changes [56]. Not only did this intervention reduce the body mass index, but also importantly resulted in amelioration of the internalizing and externalizing problems in the participants of the intervention group compared to the control group [56]. Although the biological mechanisms underlying stress-mediated pathologic conditions remain to be further elucidated, sufficient body of evidence exists supporting the notion that less chronic distress, decreased by stress management techniques, may promote health and increase longevity.

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