Early traumatic experiences and eating disorders: a focus on the endogenous stress response system

Francesca Marciello1, Alessio Maria Monteleone2, Giammarco Cascino1,2, Giuseppina Patriciello2, Francesca Pellegrino2, Gianmarco Fiorenza1, Palmiero Monteleone1

1 Department of Medicine, Surgery and Dentistry, “Scuola Medica Salernitana”, University of Salerno, Salerno, Italy; 2 Department of Psychiatry, University of Campania L. Vanvitelli, Naples, Italy.

SUMMARY

Exposure to trauma during childhood is believed to be a major risk factor for lifelong psychiatric disorders, including eating disorders (EDs). Moreover, both an association between stressful life events and the onset/maintenance of EDs and higher presence of traumatic experiences in people with EDs have been documented. The aim of this review was to summarize the current knowledge concerning mechanisms involved in the connection between early trauma exposure and the risk to develop an ED by focusing on body stress response system. Several researches confirm that childhood trauma impairs the biological response to stress so dysregulations of the activity of the hypothalamic-pituitary adrenal (HPA) axis have been proposed as one of the main mechanisms underlying the early trauma-related risk for EDs across the life span. The data presented in this review support the existence of a “maltreated ecophenotype” in EDs characterized by specific clinic and neurobiological features resulting from early stressful environmental experiences. This concept may have important implications in treatment programming for such a type of patients.

Key words: eating disorders, anorexia nervosa, bulimia nervosa, trauma, stress response, hypothalamic-pituitary-adrenal axis

Introduction

Existing literature has widely documented that exposure to childhood maltreatment increases the risk for development of different psychiatric disorders, including mood disorders, anxiety disorders, psychosis, alcohol and drug use disorders, disruptive and antisocial behavior disorders and eating disorders (EDs) later in life. On the other hand, epidemiological research has suggested that the onset of psychiatric disorders across the life course is associated to adverse childhood experiences in nearly a third of cases, underscoring the public health significance of that exposure. The reported association of childhood maltreatment with different psychiatric disorders suggests that early maltreatment can be considered a non-specific risk factor for psychopathology. Anorexia nervosa (AN) and bulimia nervosa (BN) are complex psychiatric disorders predisposing to several severe medical and psychological complications associated with high morbidity and mortality. There is a general agreement on considering behavioural anomalies of EDs as secondary epiphenomena to a more profound psychopathological core, defined by excessive concerns about body shape and weight. Thus, the core psychopathology of these disorders is characterized by a pathological fear of weight gain and alterations in the perception of body shape, thus individuals develop aberrant eating behaviors aiming at maintaining...
a low body weight. In particular, subjects with AN restrict food intake and/or perform physical hyperactivity in order to obtain and maintain a low body weight, although in some cases binge eating followed by compensatory purging or non-purging behaviors also occurs. For this reason, two types of AN are identified: the AN restrictive subtype (ANR) and the AN binge-purging subtype (ANBP) 7. BN, instead, is characterized by binge eating episodes followed by compensatory behaviors such as self-induced vomiting, misuse of laxatives and diuretics, prolonged starvation and restriction of food intake. Although a conclusive etiopathogenesis of EDs is still unknown, it is widely acknowledged that biological, sociocultural and psychological factors likely influence their development, progression and outcome. Moreover, an association between stressful life events and the onset/maintenance of EDs has been clearly demonstrated 8-11 and individuals with EDs have been shown to have experienced greater adversity over their life course. For instance, case register studies have identified specific associations between later AN diagnosis and obstetric complications such as anxiety during pregnancy, pregnancy complications, childbirth complications, infant parameters/prematurity 12,13. Moreover, during childhood, distinct types of child maltreatment, such as sexual, physical and emotional abuse or neglect, traumatic loss, and interpersonal stressors have been associated to both the onset and the maintenance of many EDs 2,14,15.

In this review we summarize the current knowledge suggesting potential mechanisms moderating the relationship between early trauma exposure and the risk to develop an ED by first describing one of humans’ basic functions: response to stressors. Moreover, we will present evidence that a “maltreated ecophenotype” can be proposed for people with EDs.

**Biological mechanisms regulating the body stress response**

Body response to real or perceived environmental stressors is regulated by an endogenous biological system, which includes the sympatho-adreno-medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis.

The SAM component of the stress response provides rapid physiological responses to potentially dangerous situations, which are responsible for the increase in heart rate and blood pressure, redistribution of blood flow to the brain and major muscle groups, and a decrease in vegetative function referred to as the “fight of flight” response 16. The reaction of the HPA axis to stress consists in a slower, sustained, and amplified physiological response through the synthesis and secretion of glucocorticoids from the adrenal cortex. Glucocorticoids increase gluconeogenesis and lipolysis, inducing mobilization of fuel from liver and from white adipose tissue in order to provide the energy necessary to cope with the stressor 17. Moreover, glucocorticoids exert a negative feedback on the HPA axis activity favouring the termination of the stress response. This feedback limits the time of tissue exposure to glucocorticoids, minimizing their catabolic, lipogenic, anti-reproductive and immunosuppressive effects 18,19.

The hypothalamic paraventricular nucleus (PVN) has a key role within the circuits regulating the endogenous stress response, since it integrates signals coming from brainstem (nucleus of the solitary tract) and forebrain limbic structures (prefrontal cortex, hippocampus, and amygdala), which are activated in response to threats to physiological homeostasis or psychogenic stressors, respectively 20. PVN neurons lead to catecholaminergic stimulation of peripheral tissues, via the sympathetic nervous system, inducing the release of catecholamines into systemic circulation by the adrenal medulla. Moreover, PVN neurons release corticotropin-releasing hormone (CRH) and arginine vasopressin from their terminals in the median eminence into the portal circulation. CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior hypophysis into systemic circulation, and ACTH stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex.

The hippocampus, via projections to the PVN nuclei in the hypothalamus, has an inhibitory role on the HPA axis activity, intervening in the glucocorticoid-mediated termination of the endogenous stress response 20.

**Childhood maltreatment and HPA axis dysregulation in mental disorders**

Understanding the processes and mechanisms that contribute to the development of mental disorders in maltreated children appears to be an essential challenge of research in order to implement efficient interventions for both prevention and treatment of psychopathological disorders.

The biological background through which trauma exposure in the childhood may predispose to the development of psychiatric disorders later in life is still unknown. In last decades, scientific research has made enormous strides in trying to clarify the potential neurobiological consequence of childhood adverse experiences. A potential picture emerging involves the relationship between early traumatic events and alterations in stress-susceptible brain regions leading to long-lasting dysregulation in the neuroendocrine stress response system 21,22. In particular, the role of the HPA axis has
been widely studied as a key determinant of psychiatric disorders onset associated with childhood trauma. Indeed, exposure to early adversities is considered a major determinant for enduring alterations of the HPA axis functioning leading to an increased sensitivity for the development of trauma-related symptoms. The hypothesis is that the childhood trauma-related alterations of HPA axis functioning reflects aspects of a biological pathway that may contributes to psychopathological dimensions in adulthood. Recent studies have attempted to clarify how the human endogenous response system reacts to early life stressors reporting long-lasting neurobiological modifications. In particular, most studies have focused on the epigenetic processes of DNA methylation (i.e., the chemical modification of DNA based at CpG islands, close to or within gene promoters) and has explored alterations in HPA axis activity in response to changes in stress-related genes’ methylation levels. In fact, regards DNA methylations levels, specific CG sites within the NR3C1 exon 1F were found positively associated to childhood emotional abuse severity. Since this was associated to higher basal HPA axis activity, authors suggested that it may reflect an acquired glucocorticoid receptor resistance. Therefore, early life experiences can influence stress sensitivity through epigenetic changes in stress-related genes, which may explain why some genetically at-risk individuals are more susceptible to some types of stress-reactive psychopathologies.

In addition, Teicher and Samson have suggested that a developmental phenotype, the “maltreated ecophenotype”, may result from structural and/or functional alterations in the brain as a consequence of early stressful environmental experiences. It has been reported that adults with a history of maltreatment had smaller hippocampi and variations in the size of the amygdala, depending on the timing of stress exposure. Furthermore, frontal cortical regions and the anterior cingulate cortex volumes are reduced in individuals with a history of maltreatment. This may contribute to the impairment in the regulation of the endogenous stress response. A controversy still exists with respect to the direction of trauma-induced changes in HPA axis functioning, since both increased and decreased HPA axis activity has been described in individuals exposed to early maltreatment. Indeed, a history of childhood maltreatment has been associated with HPA axis hyperactivity in subjects who developed depression or anxiety in adulthood as well as in healthy individuals. Therefore, higher circulating cortisol levels, enhanced cortisol awakening response (CAR), increased adrenocorticotropic hormone (ACTH) and cortisol responses to psychosocial stress or endocrine challenges (i.e., dexamethasone suppression test, DST) have been described in populations characterized by the presence of traumatic events in early life. The biological explanation of these findings could be that chronic hyperactivation of the stress system is related to hypersecretion of CRH by the hypothalamus and ACTH hypersecretion by the pituitary, resulting in higher circulating cortisol levels and to an “insensitive” negative glucocorticoid feedback of the HPA axis loop.

In contrast, other authors were in favor of a HPA axis hypoactivity in response to childhood traumatic events in psychiatric populations, reporting lower circulating cortisol levels and blunted cortisol stress responses to psychosocial stress or endocrine tests (DST, CRH test) in psychiatric patients with a history of childhood maltreatment. This diminished activity could represent a compensatory physiologic adaptation possibly related to a negative feedback hypersensitivity of glucocorticoids or a long-lasting glucocorticoid catabolism drop leading to higher active cortisol persistence in liver and kidney without elevation in the periphery. A significant factor modulating the impact of childhood maltreatment on future HPA axis activity may be its exact timing, suggesting a degree of developmental programming through glucocorticoid signaling, that is childhood traumatic experiences are probably associated with a differential impact on HPA activity according to the specific developmental period of exposure. Most researches, instead, proposed that the opposite polarities of HPA axis dysregulation could be explained by the time since the trauma exposure. In fact, recent trauma exposure has been related to an enhanced HPA axis activity whereas HPA axis hypoactivity has been associated with remote trauma exposure. As a matter of fact, children (8-12 years old) with aggressive behavior and personal history of trauma exhibited enhanced cortisol reactivity to laboratory stress that, instead, resulted reduced in female youths (12-16 years old) exposed to childhood maltreatment. Also, different types of childhood trauma have been related to distinct anomalies in HPA-axis functioning. Finally, a dose-dependent effect of traumatic experiences on different measures of HPA axis activity, such as hair cortisol, salivary cortisol, CAR, has been described by some of the authors, suggesting a higher impairment of HPA axis functioning with increasing traumatic load.

### Childhood maltreatment and eating disorders

Early maltreatment has been found significantly more frequent in people with EDs than in general population. The overall odds of having an ED has been estimated to be 3.21 time higher (95% CI [2.29, 4.51], p = 0.001) in individuals reporting a childhood trauma. A recent meta-analysis found that the prevalence of childhood maltreatment was higher in each type of EDs...
relative to both healthy controls and psychiatric control groups. Moreover, current literature suggests that the experience of distinct forms of childhood maltreatment is differentially associated with different EDs. Higher levels of childhood trauma have been found to be associated with higher levels of ED symptoms and lower daily functioning, and this association seems to be independent from psychiatric comorbidities. Moreover, a significant dose-response effect between the number of experienced trauma and ED symptoms severity has been demonstrated. Finally, compared to ED patients without a history of childhood trauma exposure, those who were exposed to early traumatic events have been shown to exhibit a higher drop-out rate from psychotherapies as well as a poorer response to cognitive behavioral therapy at 3-year follow-up, although this response has been found to be similar at 1-year follow-up between AN patients with or without childhood sexual abuse.

**HPA axis activity in EDs**

HPA axis and, in particular cortisol, have been the focus of an extensive research in EDs. Briefly, almost all studies agree in indicating that subjects with AN have elevated basal or mean daily cortisol levels due to the well-known effects of starvation and weight status on HPA axis functioning, whereas more variability exists in results on basal and mean daily cortisol levels in women with BN. In fact, biological mechanisms underlying cortisol alterations in BN are less clear, although several studies suggested that binge-purging episodes may cause elevated basal and mean daily cortisol levels. However, when the HPA axis activity has been studied by dynamic measures, such as the CAR, controversial findings have emerged. As a matter of fact, some studies showed that subjects with AN had an enhanced CAR compared to BN ones and controls whereas others reported no significant differences among groups. Another line of research has focused on cortisol reactivity to physical and psychosocial stressors in order to explore the reactivity of the of HPA axis to an acute stress. These studies have suggested the occurrence of both a blunted or an enhanced or a normal HPA axis reactivity to stressor exposure. So additional research is needed to verify which variables could explain those discrepancies, and, in this line, recent studies have explored the impact of childhood maltreatment on HPA axis activity in people with EDs.

**Early traumatic experiences and HPA axis functioning in EDs**

In order to assess the HPA axis functioning in maltreated subjects with EDs, some authors have investigated the cortisol response to the dexamethasone suppression test (DST). Basurte et al. found a significant relationship between cortisol suppression to low-dose (0.5 mg) DST and traumatic history in subjects diagnosed with ED. Similarly, Díaz-Marsá et al. reported that cortisol suppression to very low dose (0.25 mg) DST was significantly correlated with intensity of childhood traumatic experiences highlighting a hypersensitive HPA axis response to DST in maltreated ED subjects. As for BN, Yilmaz et al. have shown no differences in cortisol suppression following a DST in bulimic patients with or without a history of childhood traumatic event and reported that Childhood Trauma Questionnaire (CTQ) scores were not associated with cortisol levels following DST. Cortisol response to oral administration of the partial 5-HT agonist meta-chlorophenylpiperazine (m-CPP) was studied in bulimic women in relation to the presence of childhood abuse: BN individuals reporting childhood abuse showed a decreased plasma cortisol response to m-CPP than normal eater non-abused women. Several studies have been conducted in order to examine the effect of childhood trauma experiences on HPA axis activity in ED by measuring salivary CAR. Monteleone AM et al. reported that non-maltreated women with AN exhibited an enhanced CAR compared with controls and non-maltreated BN while subjects with AN or BN with positive history of childhood trauma exhibited statistically significant blunting of CAR than non-maltreated groups. These findings support the hypothesis that malnutrition and childhood trauma exert opposite effects (increase/blunting) on CAR in AN. Evidence for a dose-dependent effect of the traumatic load on HPA axis in women with ED were described. In fact, AN and BN subjects with history of early trauma exhibited a progressive impairment of CAR with increasing the number of reported trauma. More importantly, that study showed that although significant negative correlations emerged between the overall cortisol secretion at awakening and the different types of childhood trauma such as emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse, those correlations disappeared when a multiple regression analysis, including the number of trauma each patient was exposed to, was run. Indeed, only the number of experienced trauma persisted significantly and negatively associated to the CAR, suggesting that the number and not the type of childhood trauma is a major determinant of the impaired CAR in adult ED patients. The effects of early trauma on HPA response to an acute psychosocial stress were also investigated in AN women with history of childhood maltreatment. A blunted cortisol response to the Trier Social Stress Test (TSST) was detected in AN women exposed to childhood trauma as compared to both healthy controls and...
Early traumatic experiences and eating disorders: a focus on the endogenous stress response system

non-maltreated AN women. Moreover, Mal AN women, compared to the other two groups, displayed a significantly reduced overall cortisol increase after the TSST, but a similar amount of the overall cortisol production. Since the overall cortisol increase is an index of the sensitivity of the HPA axis to a challenge test, those results suggest that childhood trauma exposure has detrimental effects on the HPA axis reactivity to a psychosocial stressor in adults with AN. The diminished cortisol response to an acute psychosocial stressor in adult women with AN reporting childhood maltreatment is not easy to explain, although some hypotheses have been proposed. The first one suggests that, according to the allostatic theory, a prolonged hyperstimulation of the HPA axis, due to repeated stressful events during early development, may lead to a state of chronic HPA axis hypoactivity and/or hypo-reactivity. Alternatively, since a specific deficit in social information processing in maltreated children has been proposed, it has been proposed that such a deficit may be responsible for a hypo-activation of the HPA axis in maltreated AN women during the TSST, which specifically requires the use of this ability. Taken together, all these studies suggest that exposure to childhood maltreatment may be associated with long-lasting neuro-endocrine modifications, which may account for its increasing risk for ED psychopathology.

Clinical implications and conclusions

It seems likely from the above that exposure to trauma in the childhood may be responsible of long-lasting effects on the activity of the HPA axis, which could represent the biological background of an intrinsic vulnerability to deal with potential stressful life events favoring the development/maintenance of an ED. Obviously, other risk factors likely interact with this vulnerability to precipitate or maintain an ED. Anyway, the data presented in this review support the existence in EDs of a “maltreated ecophenotype” characterized by specific clinic and neurobiological features. This may have consequences on the treatment programming for those patients. Indeed, although there are few studies in literature and the results are not really consistent, it seems that childhood trauma exposure has an impact on the outcome of psychotherapeutic interventions in people with EDs. Calugi et al. reported that the 6- and 12-month clinical outcomes of an enhanced-cognitive behavioural therapy (CBT) did not significantly differ between adult AN women with childhood sexual abuse and those without such an abuse. Instead, another research group has recently reported that ED patients with childhood physical abuse had not only a more complex clinical presentation at admission but also lower ED psychopathology improvement and especially lower comorbidity remission three years after completion of a CBT programme compared to patients without a history of abuse. Furthermore, dropping out for treatment occurred more rapidly in patients with abuse than in those without abuse, and the time to drop-out resulted even shorter in those patients who have experienced both abuse and neglect in their childhood. These data are in line with a previous study showing a dose-dependent effect of the traumatic load on the drop-out from psychotherapeutic treatment in BN with an increasing dropping-out as the number of childhood trauma increased.

These findings let us to suggest a lower efficacy of the current therapies primarily focused on ED symptoms in the presence of an history of childhood maltreatment and corroborate the importance of an integrated approach for the treatment of people with EDs especially in the presence of a childhood maltreatment history. In particular, it may be important to extend intervention strategies beyond ED core symptoms, focusing on the person’s self-esteem development, abilities to recognize inner body states and emotions and on their mediating role between childhood maltreatment and ED symptoms.

References


F. Marciello et al.


43 Hinkelmann K, Muhtz C, Dettenborn L, et
Early traumatic experiences and eating disorders: a focus on the endogenous stress response system


Monteleone P, Scognamiglio P, Canestrelli B, et al. Asymmetry of salivary cortisol and α-amylase responses to...


78 Yilmaz Z, Kaplan AS, Levitan RD. The role of depression and childhood trauma on cortisol suppression in women with bulimia nervosa: a pilot study. Eat Weight Disord 2012;17:e17-21.


