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Childhood maltreatment and adult psychopathology: pathways to hypothalamic-pituitary-adrenal axis dysfunction

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Abstract

Objective—The aim of this paper was to examine the relationship between childhood maltreatment and adult psychopathology, as reflected in hypothalamic-pituitary-adrenal axis dysfunction.

Method—A selective review of the relevant literature was undertaken in order to identify key and illustrative research findings.

Results—There is now a substantial body of preclinical and clinical evidence derived from a variety of experimental paradigms showing how early-life stress is related to hypothalamic-pituitary-adrenal axis function and psychological state in adulthood, and how that relationship can be modulated by other factors.

Discussion—The risk for adult psychopathology and hypothalamic-pituitary-adrenal axis dysfunction is related to a complex interaction among multiple experiential factors, as well as to susceptibility genes that interact with those factors. Although acute hypothalamic-pituitary-adrenal axis responses to stress are generally adaptive, excessive responses can lead to deleterious effects. Early-life stress alters hypothalamic-pituitary-adrenal axis function and behavior, but the pattern of hypothalamic-pituitary-adrenal dysfunction and psychological outcome in adulthood reflect both the characteristics of the stressor and other modifying factors.

Conclusion—Research to date has identified multiple determinants of the hypothalamic-pituitary-adrenal axis dysfunction seen in adults with a history of childhood maltreatment or other early-life stress. Further work is needed to establish whether hypothalamic-pituitary-adrenal axis abnormalities in this context can be used to develop risk endophenotypes for psychiatric and physical illnesses.

Descriptors

Cortisol; Risk factor; Psychopathology; Child abuse; Hypothalamus

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Introduction

For many years, empirical observations deriving from psychoanalytic, psychotherapeutic and general psychiatric clinical settings have suggested that childhood maltreatment has long-term consequences on mental health in adulthood.[1–3] Recently, more methodologically rigorous clinical and epidemiological studies have confirmed these earlier findings, while advances in basic and applied neurosciences have led to greater insights into possible mechanisms of pathogenesis.

Psychiatric consequences of childhood maltreatment

Childhood maltreatment is a major social problem. It is common and can result in serious physical injury or even death. Moreover, its psychological consequences can acutely affect a child's mental health well into adulthood.[4] Four types of maltreatment are commonly recognized: physical abuse, sexual abuse, emotional (or psychological) abuse and neglect.

Childhood maltreatment is associated with a diverse range of psychiatric consequences. In children and adolescents, it increases the risk of behavioral problems, including internalizing (anxiety, depression) and externalizing (aggression, acting out) behavior.[5–9] Maltreated children have a moderately increased risk of depression in adolescence and adulthood (adjusted odds ratios ranging from 1.3 to 2.4), which will partly mirror the family context in which the maltreatment occured.[5,7,8,10–13]

Because depression is common, about a quarter to a third of maltreated children will meet the criteria for major depression by their late 20's,[8,14,15] thus representing a substantial public health burden. For many of the affected individuals, the onset of depression begins in childhood, hence the importance of focusing on early intervention before the symptoms of depression appear in the abused and neglected children. Depression is commonly associated with neglect and physical and sexual abuse, with no clear evidence of more specific effects of any particular type of maltreatment. Some investigators have shown a dose-response relationship, with depression more likely occurring with harsh or severe physical abuse than with less severe forms of maltreatment.[8,16] Consistent evidence suggests that both physical and sexual abuse are associated with a doubling of the risk of attempted suicide in young people who are followed up on into their late 20's. For physical and sexual abuse, these effects persist after adjustment for confounding family and individual variables[8,17] but, for neglect, these effects are mainly explained by family context.[11]

Other psychiatric disorders in adulthood that are frequently associated with childhood maltreatment include personality disorders,[18,19] alcohol abuse and dependence,[11] eating disorders,[20] anxiety disorders,[21] and posttraumatic stress disorder (PTSD).[22]

Neurobiological consequences of stress

The term *stress* has been widely used to denote an individual's response to environmental or psychosocial conditions which require change. *Allostasis* and *allostatic load* are more useful concepts for understanding the neurobiological consequences of stress. Allostasis involves the maintenance of stability (i.e., of homeostasis). The concept of allostatic load was

proposed to refer to the physiological degradation of the individual as a result of repeated cycles of allostasis, as well as to the inefficient turning-on or shutting-off of responses to stressors.[23,24] The concepts of allostasis and allostatic load invoke a cascade of cause and effect that begins with primary stress mediators, such as catecholamines and cortisol, and leads to primary effects and then to secondary and tertiary outcomes.

The brain acts as an integrative center coordinating the behavioral, neuroendocrine and other neurobiological responses of the individual to environmental challenges and internal physiological needs (e.g., thirst, hunger, sleep-wake cycle). There are considerable individual differences in coping with such challenges based upon interacting genetic, developmental and experiential factors. Moreover, there can be an amplifying effect of genetic predisposition and early developmental events, such as childhood maltreatment, thus predisposing certain individuals throughout their lives to over-react physiologically and behaviorally to events. The capacity to adapt and maintain homeostasis (i.e., allostasis) in the face of challenges and the ability to turn adaptive responses on and off efficiently are vital to survival; at the same time, excessive demand for such adaptive responses can lead to cumulative effects over long time intervals.[23,24]

These cumulative effects, i.e., the allostatic load caused by forced adaptations to various psychosocial challenges and adverse environments are manifested as a structural and functional deterioration of the organism. Among the many factors that contribute to allostatic load are genes, early experiences and early development, as well as learned behaviors reflecting life-style choices with respect to diet, exercise, smoking, and drinking. All these factors influence the reactivity of the systems that produce the physiological stress mediators. As a result, allostatic load partially reflects comes to reflect a genetically or developmentally-programmed inefficiency in handling not only unusual stressors, but also the normal challenges of daily life (e.g., thirst, hunger, need for sleep), as well as the adverse physiological consequences of an unhealthy diet, sedentariness, excessive alcohol or smoking.[23,24]

The HPA axis and psychopathology

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in major depression is suggested by a large body of research, including basal and provoked measurements of plasma HPA axis hormone concentrations, imaging of pituitary and adrenal gland volume, cerebrospinal fluid (CSF) levels of corticotrophin releasing hormone (CRH), and post-mortem measures of brain CRH receptor binding and CRH messenger ribonucleic acid (mRNA) levels.[25,26] Indeed, hyperactivity of the HPA axis as a state marker for major depression is one of the most prominent findings in psychoneuroendocrinology.[27–29] Hyperactive CRH neurons, manifested as CRH hypersecretion and impaired efficacy of the glucocorticoid-mediated feedback are considered to be reliable hallmarks of the disturbed neuroendocrine regulation associated with, and perhaps causally related to depressive disorders.[30]

Allostatic load leads to alterations in hippocampal neuroplasticity, which is partially regulated by the brain-derived neurotrophic factor (BDNF). Hippocampal neurons subjected

to an increased allostatic load show reductions in dendritic arborization and in BDNF expression, which could be one of the factors mediating the dendritic effects. The reduction in BDNF is partly mediated by excessive glucocorticoids, a characteristic feature of HPA axis hyperactivity, which can interfere with the normal transcriptional mechanisms that control BDNF expression. Decreased neurogenesis and increased rate of neuronal death and atrophy are also mediated by excessive glucocorticoids.[31] Clinical studies are consistent with these findings: depressed patients have a significant reduction in gray matter in the hippocampus, anterior cingulate cortex and dorsomedial prefrontal cortex compared to controls. The reduction is more pronounced in unremitted patients than in remitted patients.[32]

However, the relationship between HPA function and emotional disturbances involving mood and anxiety is not entirely unambiguous. For example, *decreased*, rather than increased, cortisol secretion has been reported in patients with nonpsychotic forms of major depression,[33] major depression with comorbid PTSD,[34] and atypical depression.[35] Super-suppression of cortisol in response to a low-dose of dexamethasone, as observed in abused women with depression and comorbid PTSD, is a classical feature of PTSD.[36,37]

Moreover, HPA axis dysfunction is not restricted to depressive illness, but has been linked to several other psychiatric and functional somatic disorders. A key question is whether such dysfunction operates as a pre-existing pathogenic risk factor, whether it reflects the ongoing pathogenesis of the illness, or whether it represents some combination of both.

HPA axis function in individuals with a history of childhood maltreatment

1. Studies on the pituitary–adrenal and autonomic responses to psychosocial stress

A number of studies have used structured laboratory test settings to evaluate responses to psychosocial stress. Among the most widely employed is the Trier Social Stress Test (TSST), which consists of a public speaking task and a mental arithmetic task, both standardized and conducted in front of a panel of judges. The TSST has been shown to reliably induce HPA axis and sympathetic activation.[38] Blood and/or saliva samples for the determination of plasma or salivary adrenocorticotropin (ACTH) and cortisol levels, as well as heart rate measures are obtained before, during, and after the stress induction.

In an important study, Heim et al. used the TSST to evaluate neuroendocrine and autonomic responses in four groups of women who had been carefully categorized according to the presence or absence of early-life abuse and current major depression, as follows: 1) with a history of early-life abuse and with current major depression; 2) with a history of early-life abuse and without current major depression; 3) without a history of early-life abuse and with current major depression; and 4) without a history of early-life abuse and without a history of psychiatric disorder (i.e., healthy controls).[39]

Women with a history of childhood abuse, with or without current major depression, exhibited increased ACTH responses to stress compared with controls. The net ACTH response was more than 6-fold greater in abused women with current major depression than in controls. These women also demonstrated increased cortisol and heart rate responses to

psychosocial stress. Abused women who were not currently depressed exhibited normal cortisol responses, despite their increased ACTH response, perhaps suggesting adrenal adaptation to central sensitization as a marker of resilience against depression after early stress. Depressed women without a history of abuse demonstrated normal neuroendocrine responses.

These findings, which are consistent with studies of early-life stress in laboratory animals, suggest that HPA axis and autonomic nervous system hyperreactivity, presumably due to CRH hypersecretion, may be a long-lasting consequence of childhood abuse in women and one which may constitute a risk factor for adult psychopathology.[27] Analyzing the same data using multiple regression techniques, Heim et al. showed that childhood maltreatment was the strongest predictor of ACTH responsiveness, followed by a number of abuse events, adulthood traumas and depression.[40] These findings indicate that a history of childhood abuse *per se* in women is related to increased HPA axis reactivity, which is further enhanced when additional trauma occurs in adulthood.[27]

In contrast, a more recent study by Carpenter et al. found that men and women with a history of childhood maltreatment and no history of depression had *decreased* cortisol responses to the TSST.[41] These findings are consistent with other recent studies showing attenuated cortisol responses to psychosocial or neurobiological challenge in adults with a history of maltreatment, as discussed further below.

2. Studies on the pituitary–adrenal and autonomic responses to pharmacological provocation tests

The CRH and ACTH stimulation tests, derived from classical neuroendocrinology, have also been used to explore HPA axis dysfunction related to psychopathology and associated risks factors. The former evaluates the responsiveness of the anterior pituitary to CRH, with diminished reactivity presumably reflecting downregulation of corticothrophs in response to chronically increased stimulation by the CRH-containing parvocellular neurons originating in the paraventricular nucleus (PVN) of the hypothalamic median eminence.[42] The latter evaluates the responsiveness of the adrenal cortex to its major stimulating hormone, i.e., ACTH.[43]

In their study of depressed and non-depressed women with and without a history of childhood maltreatment, Heim et al. administered both tests to the same subjects.[42,44] They found that abused women without depression exhibited increased ACTH responses to CRH, but both groups of depressed women (with and without childhood maltreatment) exhibited a blunted ACTH response to CRH, which is consistent with many previous studies of major depression.[45,46] Abused women without depression had a lower cortisol response than other groups after the ACTH stimulation test.[42] Laboratory studies on early-life stress using non-human primate models have demonstrated similar results.[47,48]

Heim et al. hypothesized that their results could reflect both a sensitization of the pituitary and a counter-regulatory adaptation of the adrenal gland in abused women without current depression. As cortisol has inhibitory effects on the central CRH and noradrenergic systems, a relative decreased availability of cortisol, as a consequence of childhood trauma, might

facilitate disinhibition of central stress responses. When subjected to even more stress, such women might then repeatedly hypersecrete CRH, eventually resulting in pituitary CRH receptor downregulation and symptoms of depression through CRH effects in extra-hypothalamic circuits.[27]

However, caution is required when interpreting such findings, as underscored by Carpenter et al., who used multiple regression analysis in an effort to disentangle the effects of depression and early-life stress on CSF CRH in adults.[49] In their study of depressed and healthy control adults, perceived early-life stress was significantly correlated with concentrations of CSF CRH, but the presence of depression was not. However, the relationship between CSF CRH and early-life stress was complex: CSF CRH concentrations were *negatively* correlated (i.e., lower) with adversity in the perinatal and pre-teen years (ages 6–13 years), but *positively* correlated (i.e., higher) with stress in the pre-school years (ages 0–5 years). These findings were interpreted in light of considerable preclinical research in laboratory animals, demonstrating that timing of exposure to stressors in early life is critically important in determining their long-term effects on neurobiology and behavior.

3. Studies on glucocorticoid receptor (GR) sensitivity using pharmacological provocation tests

Basal hypocortisolism and hypersuppresion of cortisol after low doses of dexamethasone have been observed both in patients with PTSD and in women with a history of early-life stress and PTSD.[36,50] These findings are believed to reflect increased GR sensitivity. The combined dexamethasone/CRH (Dex/CRH) test was developed to allow for a more rigorous *in vivo* examination of GR function by increasing the sensitivity of the classical dexamethasone suppression test (DST).[51] In the Dex/CRH test, CRH-induced escape of cortisol from suppression reflects impaired glucocorticoid-mediated feedback control of the HPA axis under conditions of increased hypothalamic drive.

Heim et al. used this approach to study HPA axis function in men with and without major depression and childhood abuse.[52] Abused men demonstrated increased cortisol responses compared to non-abused men, regardless of the presence of major depression. Increased responses were associated with exposure to both sexual and physical abuse, and were correlated with the severity of abuse. Their results suggested that childhood maltreatment is associated with impaired glucocorticoid-mediated feedback control of the HPA axis under stimulated conditions.

Similar results have been reported for women with borderline personality disorder. Rinne et al. compared borderline personality disorder patients with and without sustained childhood abuse and comorbid PTSD or major depression with healthy control subjects.[53] The borderline patients who had been chronically abused had increased ACTH and cortisol responses to the Dex/CRH test; the presence of comorbid PTSD significantly attenuated the ACTH response.

Once again, however, specific factors relating to the nature of the abuse can markedly affect the results of such studies. Carpenter et al. recently reported their findings with the

Dex/CRH test in a large sample of 230 adults without major Axis I disorders.[54] Using a general linear models analysis, the authors tested for a large number of potentially confounding variables, including age, gender, education level, socioeconomic adversity in childhood, current depressive and anxiety symptoms, smoking, exogenous hormone use (for contraception or estrogen replacement) and types of maltreatment. They found that a history of self-reported childhood emotional abuse was independently and significantly associated with diminished cortisol response to the Dex/CRH test, whereas physical abuse, sexual abuse, emotional neglect and physical neglect had no significant independent effects.

Currently available studies indicate that much still remains to be learned about the different clinical factors that affect GR function in humans and how this process takes places. At the same time, recent preclinical research has shown, more clearly than ever, how GR function could be implicated in the pathogenesis of HPA axis dysfunction in clinical settings. For example, early adversity in rodents induces reduced expression of GR's at the epigenomic level by inducing DNA methylation at a promoter site of the GR gene.[55,56] It would be logical to expect that the impaired glucocorticoid effects resulting from this may contribute to increased stress reactivity and promote symptoms of depression.[57]

Long-term sequelae of early-life stress: moderating and mediating factors

As is evident from the preceding discussion, the ultimate effects of childhood maltreatment in terms of HPA axis function and psychiatric outcome in adulthood reflect a complex interplay of other moderating and mediating conditions. Elucidation of these factors and the nature of their relationships with adulthood outcomes is a major challenge.

For example, clinical experience and the preclinical animal literature suggest that early developmental events can have a major impact on subsequent psychological and neurobiological function. We recently studied 42 premature infants born at 33.3±1.9 weeks gestation of whom 15 were maintained in incubators for least 2 weeks and 27 were cared for with the kangaroo method, in which infant and mother consistently maintain skin-to-skin contact using specially-applied bandages (Mello et al., unpublished data). Groups did not differ with respect to gender, socioeconomic status, birth weight, gestational age or age at evaluation. We hypothesized that incubator care could serve as a naturalistic human model of maternal deprivation. Regression analysis showed that, at the age 6 months, infants who had been placed under incubator care/who had received care through an incubator had higher awakening salivary cortisol concentrations and were shorter compared to those receiving the kangaroo method. There were no differences in weight or cognitive and psychomotor development. These results are consistent with studies in laboratory animals showing that experimental early maternal deprivation increases HPA axis activity, which could in turn be a risk factor for psychiatric illness.

Similarly, late life events in an individual's personal history can also promote risk or resilience to the development of psychopathology. Tyrka et al., while studying ACTH and cortisol responses to the Dex/CRH test in healthy adults with or without a history of parental loss found that the former group had increased cortisol responses, an effect that was particularly robust in men.[58] However, levels of parental care moderated the effect of loss:

subjects with parental desertion and very low levels of care had attenuated cortisol responses. ACTH responses did not differ between groups.

Finally, it should be noted that moderating and mediating factors need not only be extrinsic events in an individual's history as they can also be intrinsic. Tyrka et al. used the TSST and the Dex/CRH test to evaluate the effects of temperament on HPA axis in healthy adults without significant psychopathology.[59,60] They found that in both psychosocial stress and pharmacological challenge tests, those with inhibited temperament (low novelty-seeking behavior) had higher cortisol responses compared to those with high novelty-seeking behavior.

The HPA axis and genetics

If HPA axis function can be affected by an individual characteristic such as temperament, which is, in itself, complexly reflective of both constitutional and early experiential factors, it should be obvious that genetic influences on the HPA axis are likely to be significant. Empirical demonstrations of such influences in humans have begun to appear. For example, Baghai et al. demonstrated that the angiotensin converting enzyme (ACE) insertion/deletion polymorphism significantly altered the cortisol response to the Dex/CRH test in patients with major depression, with insertion homozygotes showing higher cortisol responses than deletion homozygotes; differences were no longer evident after successful antidepressant treatment.[61] Similarly, Wust et al. showed that glucocorticoid receptor gene polymorphisms determined the cortisol response to both provocative pharmacological testing and psychosocial stress, as measured by the TSST.[62]

Genetics and the long-term sequelae of early-life stress

Contemporary work on the interaction of genetics and stress has been profoundly influenced by the findings of Caspi et al., who studied a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) in a sample of 847 children who were followed prospectively from ages 3 to 26 years.[63] Individuals with one or two copies of the short allele of the polymorphism were more likely to develop depression and related symptoms in response to stressful life events than were individuals who were homozygous for the long allele. This study has been one of the most convincing empirical demonstrations to date of the gene-environment interaction in the pathogenesis of psychiatric illness. Kaufman et al. extended these findings to maltreated children, showing that low social support and the short allele of the 5-HTTLPR polymorphism interact with each other to incur in the greatest risk for depression.[64]

Barr et al. addressed the interaction of genetics and early-life stress in modulating HPA axis function in a study of ACTH and cortisol responses to stress in rhesus macaque monkeys.[65] They found that the genotype of the rh5-HTTLPR polymorphism (which is orthologous with the 5-HTTLPR polymorphism in humans) and rearing condition independently influenced HPA axis responses to stress. Moreover, rearing, rh5-HTTLPR genotype and sex interacted with one another: adverse rearing conditions and the rh5-HTTLPR short allele resulted in lower cortisol responses to stress in females, but not in males. More recently, Bradley et al. have extended this work to genes that directly control HPA axis function, demonstrating that

reported childhood abuse interacts with single nucleotide polymorphisms (SNPs) in the CRH Type I receptor gene, thus allowing for the prediction of depressive symptoms in adulthood.[66]

Exciting preclinical studies have begun to elucidate the molecular basis of such findings, showing that environmental factors are actually capable of altering gene expression. This reflects recent advances in the field of *epigenetics*, the study of how differences in phenotype and gene expression can be caused by changes in chromosome or chromatin packaging (as opposed to by changes in the DNA sequence). There is emerging evidence that such changes can remain stable between cell divisions, and might show transgenerational inheritance.

In their review of the role of epigenetics in psychiatric disorders, Tsankova et al. illustrated the significance of such findings by providing the example of BDNF. This protein has been extensively implicated in the pathophysiology of depression and the mechanism of action of antidepressant treatments, and recent work has focused on the regulation of its gene, *bdnf*.[67] Studies using an animal model of depression (chronic defeat) have shown that, in a controlled environment with no stress, *bdnf* chromatin demonstrates moderate histone H3 acetylation and no histone H3-K27 dimethylation. In this state, histone deacetylase 5 (HDAC5) represses unnecessary activation of BDNF and maintains chromatin balance. The stress of chronic defeat induces the dimethylation of histone H3-K27, resulting in a “closed” chromatin state at *bdnf* promoters and repression of *bdnf* transcript expression. Imipramine treatment after defeat stress down-regulates *Hdac5* gene expression and increases H3 acetylation, “reopening” the repressed chromatin state and reactivating transcriptional activity of the *bdnf* gene. In other words, an experiential factor (chronic defeat stress) alters BDNF function by physically modifying its gene, an effect which can, in turn, be reversed by antidepressant treatment.

Determinants of HPA axis function following early-life stress

To do a review, it is essential to recognize that, although the effects of early-life stress on the HPA axis are now well documented, such effects cannot be thought of in simplistic or bivariate terms. Rather, the understanding of these effects requires that a broad range of factors that can exert their influence via the stressor, the HPA axis, or the interaction of the two be systematically considered.

For example, above, we have considered evidence that *timing of the stressor* may be of importance, where attenuated HPA function appears following preschool stressors and enhanced function following preteen stress.[68,69] The *nature of the stressor* is relevant, with some studies suggesting increased HPA reactivity following early-life physical or sexual abuse or parental loss, but diminished reactivity following emotional abuse. At the same time, these effects can be *moderated or mediated by other factors* such as parental desertion or neglectful care (decreasing reactivity), inhibited temperament (increasing reactivity) or advancing age (decreasing reactivity). *Comorbid psychiatric conditions, recent stressors,* and *genetic vulnerability* also clearly impact HPA axis responsivity.

These factors are all, of course, extrinsic to the HPA axis itself. Divergent findings across and even within studies have underscored the fact that the way in which the "HPA axis function" is evaluated depends on which *specific parameters* are assessed. Such parameters include the *tissue* being assayed (e.g., brain, CSF, blood, saliva, lymphocytes), the *biochemical substance* being measured (e.g., mRNA, receptors, CRH, ACTH, cortisol), the *experimental method* employed (e.g., basal vs. provocative [e.g., TSST, Dex/CRH]), and the *index* used for analysis (e.g., peak change, recovery, area-under-the-curve [AUC]).

Conclusion

Risk for adult psychopathology is related to a complex interaction of multiple experiential factors: prenatal, perinatal, past environmental, and current environmental. Specific genes confer susceptibility to certain kinds of experiential factors that can lead to or modulate HPA axis dysfunction and psychopathological/psychopathology risk. HPA axis response to stress can be thought of as a mirror of the organism's response to stress: acute responses are generally adaptive, but excessive or prolonged responses can lead to deleterious effects. These deleterious effects, which may not be clinically obvious, have the potential to serve as endophenotypic markers of susceptibility to disease. Early-life stress in rodents, nonhuman primates and humans (including childhood maltreatment) alters HPA axis function and behavior, but the specific pattern of HPA dysfunction and probably the nature of the adult psychopathology are reflective of both the characteristics of the stressor and an array of modifying factors.

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