REVIEW ARTICLE

The impact of childhood maltreatment on biological systems: Implications for clinical interventions

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Childhood maltreatment represents a significant risk factor for the development of a number of mental and physical health outcomes. Converging evidence suggests that early adversity induces significant and persistent biological changes in individuals ('biological embedding'). The present review focuses on the impact of childhood maltreatment on the hypothalamic-pituitary-adrenal axis and immune system function in both children and adults. Research suggests that childhood maltreatment is associated with hypothalamic-pituitary-adrenal axis dysregulation and diurnal cortisol profiles, as well as stress reactivity. Furthermore, childhood maltreatment is associated with disruptions in various immune system markers including pro- and anti-inflammatory substances, and markers of cell-mediated immunity. The potential of interventions to reduce these negative biological effects in maltreated children is also discussed.

Key Words: *Childhood maltreatment; Cortisol, HPA axis and immune system; Interventions*

Les conséquences de la maltraitance pendant l'enfance sur les systèmes biologiques : les répercussions sur les interventions cliniques

La maltraitance pendant l'enfance constitue un important facteur de risque d'apparition de plusieurs problèmes de santé physique et mentale. Selon des données convergentes, l'adversité tôt dans la vie suscite des changements biologiques importants et persistants (le « conditionnement biologique »). La présente analyse aborde les conséquences de la maltraitance pendant l'enfance sur l'axe hypothalamo-hypophyso-surrénalien et la fonction immunitaire chez les enfants et les adultes. Selon les recherches, la maltraitance pendant l'enfance s'associe à une dysrégulation de l'axe hypothalamo-hypophyso-surrénalien et sur les profils de cortisol diurnes, ainsi que sur la réactivité au stress. De plus, la maltraitance pendant l'enfance s'associe à des perturbations à divers marqueurs du système immunitaire, y compris les substances pro-inflammatoires et anti-inflammatoires, ainsi qu'à des marqueurs d'immunité à médiation cellulaire. Le potentiel d'interventions pour réduire ces effets biologiques négatifs chez les enfants maltraités est également abordé.

Childhood maltreatment represents a significant risk factor for the development of a number of mental and physical health outcomes. Individuals who experience childhood maltreatment are at greater risk for depression, post-traumatic stress disorder (PTSD), anxiety disorders, and alcohol and drug dependence (1), as well as cardiovascular disease, gastrointestinal and metabolic disorders, and neurological, musculoskeletal and respiratory problems (2). Converging scientific evidence suggests that early adverse experiences, such as childhood maltreatment, become 'biologically embedded' into multiple systems, altering brain function, neuroendocrine responses to stress and immune system function (3,4) (Figure 1). Collectively, these findings indicate that the root of many adult diseases originates in early childhood during sensitive periods of development when biological systems are most susceptible to adverse environmental conditions. Identification of the underlying mechanisms linking childhood maltreatment to poor health outcomes is essential to characterize vulnerability to disease, and to further our understanding and capacity to intervene early. While several recent reviews provide a broad focus on the impact of early adversity on biology, the purpose of the present review is to provide a summary of recent research specifically examining the impact of childhood maltreatment on two biological systems relevant to health outcomes – the hypothalamic-pituitary-adrenal (HPA) axis and the immune system.

HPA AXIS DYSREGULATION ASSOCIATED WITH CHILDHOOD MALTREATMENT

The HPA axis coordinates the adaptive responses of organisms to any type of stressor. It functions to regulate homeostasis in the face of a dynamic and changing external milieu. The stress response 'sets off' a biochemical cascade in which corticotropin-releasing hormone is released from the hypothalamus. The release of corticotropin-releasing hormone stimulates the secretion of adrenocorticotropin-releasing hormone from the anterior pituitary which, in turn, stimulates the release of glucocorticoids from the adrenal cortex (cortisol in humans). Glucocorticoids regulate energy substrate availability and utilization, and provide negative feedback to the stress system, signalling multiple levels to decrease production of their respective hormones. In addition to its response to stress and challenges, the HPA axis exhibits a 24 h circadian rhythm in which secretion of cortisol is highest in the morning, with a gradual decline throughout the late afternoon and evening. While activation of the stress system is considered to be an essential adaptive mechanism in response to challenges, prolonged activation of this system increases vulnerability to diseases.

Child maltreatment represents an environmental stressor that alters HPA axis activity. Studies have examined the effects of childhood maltreatment on HPA axis function in children (5) and adults (6). For the purposes of the present review, to highlight complementary research in both children and adults, only studies examining diurnal rhythms and response to psychosocial stressors are reviewed. Studies regarding pharmacological stimulation are reviewed elsewhere (5,6).

In children, the majority of studies have examined diurnal cortisol levels as opposed to pharmacological stress tests due to practical and ethical considerations. Several studies report elevated cortisol levels (7-9), while others report lower levels of morning cortisol and a flatter diurnal slope (10-12). These contradictory findings may be explained by the presence of a psychological disorder, maltreatment type or timing of the abuse, or timing of cortisol sampling (developmental period). For example, higher levels of cortisol have been found in maltreated children with PTSD (7,8) and maltreated children with clinic-level internalizing problems (10,13). In contrast,

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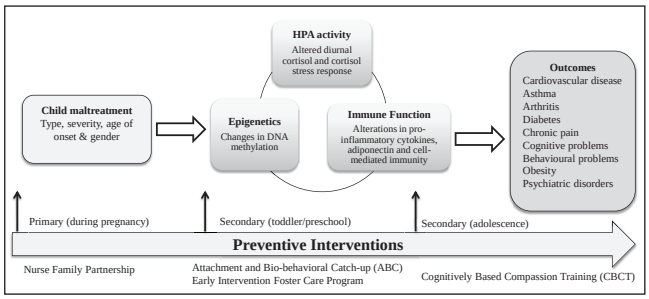

Figure 1) *Overview of the impact of child maltreatment on later outcomes and the mediating role of biological systems. HPA Hypothalamic-pituitary-adrenal*

lower levels of prosocial behaviour and higher aggression (13), comorbid internalizing and externalizing problems (9), depression and internalizing symptoms (12) have been associated with lower morning cortisol levels and an atypical diurnal decline (higher afternoon levels). In addition, maltreatment subtype may also influence the direction of cortisol findings. Although maltreatment subtypes frequently co-occur, few studies have attempted to determine the impact of maltreatment type on diurnal cortisol function. Lower morning cortisol levels have been associated with physical abuse (14) and physical neglect (10), whereas children experiencing multiple abuse types (sexual and physical abuse, as well as neglect and emotional abuse) (14) and those with reports of severe emotional abuse (10) have higher morning cortisol levels.

Finally, a third influencing factor on the direction of diurnal cortisol patterns is the timing of maltreatment and when cortisol levels are assessed. Although animal studies suggest that timing of early adversity is a crucial factor in neuroendocrinological outcomes due to the highly plastic nature of the HPA axis early in life (5), few studies have addressed this issue in the context of child maltreatment. One study demonstrated that school-age children experiencing sexual and physical abuse in the first five years of life who had high internalizing symptoms exhibited a flattening of cortisol levels across the day compared with children who were maltreated after five years of age and a group of nonmaltreated control children (12). In addition, developmental timing of cortisol sampling may make a difference in diurnal trajectories. In a longitudinal study following a large cohort of females from six to 30 years of age, patterns of attenuated diurnal cortisol levels emerged in adolescence, with significantly lower levels appearing in adulthood in females who experienced substantiated childhood sexual abuse (15).

In agreement with the latter evidence in children, adults with a history of childhood maltreatment consistently demonstrate lower morning cortisol levels and a flattening of the diurnal cycle (16-18). Lower afternoon and evening cortisol levels were reported in abused women with a history of PTSD compared with nonabused control groups (16,17). In addition, in a longitudinal epidemiological study following a cohort of individuals from childhood to middle age, high levels of reported maltreatment were associated with lower cortisol levels 45 min after awakening in both men and women, and a less steep morning decline in cortisol levels in women, but not in men (18). Collectively, these studies on diurnal cortisol suggest that the association between childhood maltreatment and HPA dysregulation emerges in childhood (as early as six to seven years of age) and can persist into adulthood. These flattened diurnal cortisol patterns have important implications for later physical and mental health outcomes (6,19).

Maltreated children, adolescents and adults also exhibit HPA axis dysregulation in response to standardized, laboratory-based psychosocial stressors. Typically, the stressors are evaluative in nature, involving public speaking and an arithmetic calculation in front of a small panel of strangers. In response to a psychosocial stressor, attenuated stress responses were observed in a group of female adolescents referred from Child Protective Services (20), and in a sample of maltreated and bullied children (21). These blunted cortisol levels were associated with more social and behavioural problems (21), but not with internalizing symptoms or current PTSD or depression (20,21). In adults, findings for cortisol stress response to a psychosocial stressor are mixed. Blunted cortisol levels have been reported in some studies (22), whereas others found markedly increased cortisol responses in women with histories of physical and sexual abuse (23). Although the nature and severity of childhood maltreatment across discordant studies appears to be similar, the presence, type and severity of psychopathology differ across studies and may contribute to inconsistent findings. Inconsistent findings may also be attributable to nonstandardized procedures across studies, such as time of day of collection and baseline collection, as well as demographic factors such as sex and race. Further research in this area is required to tease apart these confounding factors.

These alterations in HPA axis function have important implications for immune system function, and the development of autoimmune disorders and risk of infections. While there are multiple hormonal and molecular mechanisms, the HPA axis and glucocorticoids play a major role in regulating immunity (4,6).

IMMUNE SYSTEM ALTERATIONS ASSOCIATED WITH CHILDHOOD MALTREATMENT

The immune system is the body's first line of defense against pathogenic organisms (4). In response to both immune threats and stress, inflammatory responses are activated through the release of pro- and anti-inflammatory substances. These inflammatory processes have been implicated in the pathophysiology of depressive disorders, cardiovascular and immune disease, and PTSD symptoms in children and adults (6). Various measures of immune function including proinflammatory markers (eg, C-reactive protein [CRP] and interleukin-6), anti-inflammatory substances (eg, adiponectin) and cell-mediated immunity (eg, Epstein-Barr virus [EBV] and herpes simplex virus [HSV]), have all been investigated in the context of exposure to childhood maltreatment.

Several studies have found elevated levels of CRP in maltreated children (24) and in adults reporting a history of childhood maltreatment (25,26). Specifically, physically abused 12-year-old children who were currently experiencing depression had significantly higher levels of CRP compared with control children (24). Consistent with these findings, in adulthood, a history of childhood maltreatment has been associated with increased concentrations of interleukin-6 in response to a psychosocial stressor (25) and elevated baseline levels of CRP, fibrinogen (a plasma glycoprotein that plays a role in inflammation) and white blood cell counts (26). However, when examining specific types of childhood maltreatment in a sample of women, only childhood sexual abuse was significantly associated with elevated levels of CRP and interleukin-6; childhood physical abuse was associated with increased levels of these proinflammatory makers, but the increase was not statistically significant (27). Importantly, the levels of proinflammatory markers were 20% to 50% higher in women reporting a history of childhood sexual abuse compared with control women. This elevation translates into an approximate 40% to 60% higher risk for coronary artery disease (27). These estimates are consistent with longitudinal findings that at 32 years of age, individuals who experienced maltreatment in childhood are at greater risk for age-related disease risk (increased risk of depression, clustering of metabolic markers such as being overweight, high blood pressure, high cholesterol and increased levels of CRP), regardless of family risks for disease, adult socioeconomic status or health behaviours (28).

A second marker of immune system function is adiponectin, a metabolic modulator that inhibits the secretion of proinflammatory cytokines from endothelial cells. In a general population study of adults with a history of adverse mental symptoms, individuals who reported a history of childhood maltreatment exhibited lower levels of serum adiponectin (29). These findings suggest that childhood maltreatment contributes to a compromised anti-inflammatory buffering system, which may increase the risk of developing depression, cardiovascular disease and other metabolic syndromes. Finally, the third marker of immune system function, cell-mediated immunity, is indirectly measured through antibody responses to herpes viruses (eg, EBV and HSV). Adolescents with substantiated physical abuse who were currently residing with their families exhibited higher levels of antibodies related to HSV-1 compared with healthy control participants (30). An epidemiological study involving a large representative sample of young adults found that individuals reporting a severe history of childhood sexual abuse exhibited elevated EBV antibody levels compared with individuals reporting no abuse (31). Furthermore, among individuals reporting childhood physical abuse, those reporting earlier abuse (three to five years of age) exhibited higher levels of EBV antibodies compared with individuals reporting the first incidence of abuse during adolescence (31). Significant differences between groups across both studies remained even after controlling for other demographic risk factors (eg, parental education and income). Collectively, these studies highlight the pervasive and enduring effects of childhood maltreatment on multiple aspects of the immune system, which ultimately contribute to the increased risk of chronic disease later in life.

THE ROLE OF EPIGENETICS

Epigenetic modification refers to alterations in how genes function without changing the underlying DNA sequence. While epigenetic alterations of DNA can occur in a variety of ways, DNA methylation is one of the most studied epigenetic mechanisms in mammals (32). DNA methylation refers to the modification of the DNA molecule itself through alterations of the methyl molecule on the nucleotide bases (32). Although the complexity of epigenetic changes is beyond the scope of the present review, it is important to note that there is mounting evidence suggesting that early adversity is associated with alterations in DNA methylation, and that these changes have important implications for HPA axis function and immune system activity (32,33). Studies have shown that a history of childhood maltreatment was associated with altered methylation in the glucocorticoid receptor gene (34). The glucocorticoid receptor gene is involved in the stress response and is also implicated in numerous psychiatric disorders. More recently, genome-wide studies have shown that childhood maltreatment (35) and foster care placement (32) were associated with widespread differences in methylation. Collectively, these findings provide preliminary evidence that exposure to childhood maltreatment is associated with differential methylation of genes involved in the stress-response system and immune system function, as well as genes implicated in psychiatric disorders and chronic illnesses (32,35).

INTERVENTIONS

Overall, the findings summarized in the present review highlight the importance of early preventive intervention for maltreated children to alter trajectories of risk and to possibly circumvent the biological embedding of disease. The dysregulation of HPA axis activity described in maltreated children may be modified by improving the sensitivity and responsiveness of caregivers, or through placements in environments fostering warm, healthy and positive relationships. Family-based interventions with infants, toddlers and preschoolers in foster care, such as the Attachment and Biobehavioral Catch-up program (36) and the Early Intervention Foster Care program (37), were both effective in increasing morning cortisol levels and diurnal variation in cortisol levels. A third study found that within maltreating families, infants whose mothers were randomly assigned to a child-parent psychotherapy intervention or to a psychoeducational parenting intervention showed increased levels of morning cortisol levels over time compared with infants whose mothers were receiving standard community services (38). Importantly, beginning at the midintervention point, infants' morning cortisol levels in the intervention group became indistinguishable from infants from nonmaltreating families, whereas infants in the community standard care group progressively exhibited lower cortisol levels over time. These findings were maintained at a one-year postintervention follow-up. A study of adolescents in foster care enrolled in a Cognitively Based Compassion Training program found that within the intervention group, practice sessions were associated with decreased CRP levels from baseline to the six-week assessment (39). These findings suggest that the degree of engagement in the program was the influencing factor on inflammation levels within this high-risk group. Despite these impressive findings, the impact of interventions on biological systems is relatively understudied. Little is known about the effects of foster and kinship care and open adoptions on biological systems. In addition, childhood neglect is relatively understudied. Collectively, there is evidence suggesting that psychosocial or cognitively based interventions have the potential to circumvent the negative impact on biological systems associated with childhood maltreatment. In 2011, a statement issued by the Early Years Task Force of the Canadian Paediatric Society made four recommendations (40). One of the key recommendations was for governments to "invest in effective early child development interventions that maximize the health, well-being and education of all Canadian children". In this regard, there is one preventive intervention, the Nurse Family Partnership (NFP), with the best evidence for preventing child maltreatment (41). The NFP program is an evidence-based population health intervention that is internationally recognized as a gold standard for home visitation services for vulnerable populations of low-income young mothers and their children. Unfortunately, the NFP is not yet available in Canada, with only a randomized controlled trial underway in British Columbia. The lack of availability of evidence-based intervention in Canada suggests a crucial advocacy role for paediatric health care professionals. Future research on evidence-based intervention is critical. Longer-term follow-up and an expansion of biomarkers and outcome measures is needed to provide further substantiation of the effectiveness of interventions in reversing the biological embedding of disease associated with child maltreatment.

KEY MESSAGES

- Childhood maltreatment represents a significant risk factor for the development of a number of mental and physical health outcomes.
- Childhood maltreatment has an enduring impact on HPA axis and immune system function throughout development and into adulthood.
- The impact of maltreatment on health outcomes is likely mediated by these changes in biological systems.
- Knowledge of biology informs the timing and effectiveness of preventive interventions.
- Given the medical implications of maltreatment, physicians are often in a unique position to play a first-response role in identification, assessment and advocacy.

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