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Review

The biological correlates of childhood trauma in first episode psychosis

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SUMMARY

Objective

To overview biological mechanisms connecting childhood trauma to the development of psychosis.

Methods

We reviewed the evidence regarding biological correlates associated with childhood trauma in individuals affected by first episode psychosis (FEP) in terms of: 1) Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels; 2) gene × environment interaction, epigenetic and gene expression modifications and 3) metabolic biomarkers.

Results

Childhood trauma and early psychosis even when explored separately were found associated with several biological correlates. Regarding the immune system activity, in terms of both HPA axis functioning and cytokines levels, FEP patients exposed to childhood trauma showed 1) a less reactive HPA axis, characterized by a blunted cortisol awakening response, and higher serum levels of Tumor necrosis Factor-α (TNF-α) and C-reactive protein (CRP) in comparison with patients without childhood trauma. Genetics and epigenetics were also proven significantly different in traumatized FEP in comparison with non-exposed individuals. Specifically, first 2) the Val/Val genotype at the Val158Met polymorphism in the COMT gene, the A allele at rs4713916 and rs9296158 single nucleotide polymorphisms (SNPs) and the TT homozygosis at rs1360780 SNP in the FKBP5 gene were demonstrated to be risk factors for psychosis in traumatized individuals. Second, childhood trauma in FEP was proven significantly associated with global DNA hypo-methylation and lower BDNF gene expression. Finally, regarding metabolic changes associated with childhood trauma in FEP 3) higher levels of glycated hemoglobin and higher c-peptide and insulin levels were proven in patients exposed to childhood trauma in comparison with those without childhood trauma.

Conclusions

This review has given evidence regarding associations between childhood trauma and its biological correlates in first episode psychosis. Nonetheless, future studies are warranted to investigate putative biological mediators and their temporal sequence in order to elucidate developmental trajectories.

Key words: childhood trauma, first episode psychosis, epigenetic, HPA, cytokines, metabolism

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Conflict of interest
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Introduction

Childhood trauma is a complex phenomenon, significantly conditioned by bio-psycho-sociocultural elements. In Italy, almost one children out of 100 (9.5‰) is victim of maltreatments: among them, 6.9 and 4.2% refers physical and sexual abuse respectively, 13.7% reports psychological abuse, while 47.0% relates neglect, both physical and emotional[1]. The effects of childhood trauma can last a lifetime. Adults who were abused or neglected as children have a higher risk of perpetrating or being a victim of violence, becoming obese [2] or developing severe mental disorders, such

as schizophrenia [3,4]. In the general population, individuals recalling a history of childhood trauma show a threefold risk to undergo psychotic like experiences in their adulthood [5]. In turn, individuals affected by psychosis show an increased rate of childhood trauma up to the 47% of cases [4]. Specifically, 26, 39 and 34% of patients affected by psychosis refer sexual, physical and emotional abuse during childhood [6]. Female patients appear to be particularly vulnerable, showing the highest rates of sexual abuse (47.7%), and physical abuse (47.8%)[3]. Moreover, first episode psychosis (FEP) patients showed a two-fold higher prevalence (85.7 *vs* 38.7%) of childhood trauma when compared with healthy controls [7]. Severe sexual abuse was reported in 15.0-18.2% of FEP individuals, while severe physical abuse in 15.2-21.6% [8,9]. Indeed, childhood abuse has been associated with younger age of onset, earlier first admission, double hospitalization rate [4], more severe positive and dissociative symptoms [3], worse cognitive performance, lower quality of life and more deteriorated social-relational functioning [4].

Any reasonable theory that aims to explain how childhood traumatic experiences might favor later on the development of psychosis should account an integrated bio-psycho-social approach. Several paradigms have been developed focusing on diverse elements such as the stress response system, psychological elements, and environmental factors [10]. From a biological point of view, hypothalamic-pituitary-adrenal (HPA) axis functioning and cytokines levels, genetics, epigenetics, and proteomics (including biomarkers related to glucose metabolism) have been investigated to better understand the association between childhood trauma and psychosis.

The main aim of this narrative review is therefore to provide an overview of the potential biological mechanisms connecting the exposure to childhood trauma to the development of psychosis. We thus summarized the evidence related to specific biological correlates associated with childhood trauma in individuals affected by first episode psychosis. Specifically, we reviewed evidence on the role of 1) HPA axis functioning and cytokines levels, 2) gene × environment interaction, epigenetic and gene expression modifications and on 3) the levels of metabolic biomarkers within the association childhood trauma-psychosis.

Results

Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels

It has been clearly identified a key role for stress in the development and course of many psychiatric disorders, including psychosis. A dysfunctional activation of the immune system may in fact represent a potential biological mechanism connecting childhood trauma to psychopathology [11]. An altered HPA axis functioning has been found significantly associated with both childhood trauma and psychosis. HPA axis is in fact a key element of the body system that modulates the response to stress [12]: in physiological conditions, cortisol, which is the primary hormone released by the HPA axis in response to stress, functions to maintain homeostasis [13]. In case, however, of prolonged or abnormal stimulation this homeostatic mechanism may fail, resulting in increased levels of circulating corticosteroid hormones, due to an altered HPA cortisol-axis negative feedback mechanism and mediated, at least in part, by glucocorticoid receptor resistance. To date, our understanding about HPA axis functioning in FEP patients exposed to childhood trauma is hampered by mixed findings, possibly due to heterogeneous samples, different assay cortisol methodology (saliva or blood), as well as the broad definition of childhood trauma (subtype, timing, duration) [14]. HPA-axis dysfunction was proven associated to first episode psychosis itself. Specifically, HPA-axis hyperactivity, characterized by high cortisol levels in basal condition, and a blunted HPA axis response to stress (hypo-reactivity), have been both found to characterized psychosis [7,15-17]. This basal overactivity of the HPA axis in FEP patients was found in several studies, but not in all [7,15-17]. Moreover, in a recent meta-analysis [18], elevated blood levels of cortisol were demonstrated in individuals with FEP, providing further evidence for abnormal HPA axis function in early psychosis. Both HPA axis hyper- [19-21] and hypo-activation [12] and hyper- [22] and hypo-reactivity to stress [23, 24] have been significantly associated to childhood traumatic experiences. Regarding childhood trauma in FEP, a less reactive HPA axis, characterized by a blunted cortisol awakening response, might represent one of the biological mechanisms involved in the development of psychosis in individuals exposed to severe childhood trauma [25]. However, whether HPA axis dysfunction mediates the childhood trauma-FEP association or represents a trait of illness is still a matter of debate. Nonetheless, several findings [19-21] indicate that abnormalities in the stress response system, and the subsequent increased inflammation, originate in childhood and might be considered a 'biological scar' of the early exposure to high levels of stress [11].

Enhanced peripheral immune activation potentially plays a key role too in the pathogenesis of psychosis. An intricate network of interactions exists between the immune system and the central and peripheral nervous systems [26]. Inflammatory cytokines, including IL-1, IL-6 and TNF-α, represent the main mediators of this network. Cytokines are in fact responsible not only for the

organization of the cellular response to the pathogenic stimulus, but also for the behavioral changes necessary to healing. In physiological conditions, an acute stress activates the secretion of pro-inflammatory cytokines. The physiological cytokine-mediated pro-inflammatory response is temporary and strictly regulated by a balanced anti-inflammatory mechanism. Indeed, under normal conditions a neuro-immuno-endocrine anti-inflammatory response occurs. An adaptive behavioral response also takes place; it is usually temporary and placed under the control of CNS. Thus, a very complex, two-way neuro-immuno-endocrine interaction between the central and peripheral stress system and the immune axis takes place [27-29]. However, if the phlogistic stimulus becomes chronic and/or excessive it can lead to an out-of-control reaction of the inflammatory system, resulting in the development of immune-endocrine disorders (eg excessive production of proinflammatory cytokines and/or HPA axis malfunction) and contributing to the occurrence of non-functional behaviors. They therefore lose their adaptive purpose and sometimes become clinically relevant and attributable to psychiatric syndromes [26]. Cytokines are able to reach the brain through humoral, neural and cellular mechanisms [30], spreading the effect of peripherally produced cytokines on the CNS. Neurons, microglia and astrocytes, are therefore activated and an inflammatory state established. These neural inflammatory subjects, organized in complex systems, seem potentially involved in the development of psychiatric syndromes [31]. A meta-analysis of FEP studies [32] suggests the presence of an inflammatory syndrome in first episode psychosis, characterized by increased levels of IL-1α, IL-6, IL-12, IL-17, sIL-2R, interferon (IFN)-α, TNF-α, (TGF-α). Some cytokines (IL-1α, IL-6, and TGF-α) may represent state markers for acute exacerbations, and others (IL-12, IFN-c, TNF-α, sIL-2R) can be considered trait markers of psychosis [32]. Most interestingly, inflammatory markers were demonstrated particularly higher in those FEP patients who had also experienced childhood trauma [33,34]. Indeed, childhood trauma appears to be an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammation in adulthood [35]. A state of sustained peripheral inflammation follows exposure to childhood trauma [11], resulting in a chronic immune activation throughout adult life [21]. A recent meta-analysis [11] reported significantly higher levels of CRP, IL-6, and TNF-α in individuals exposed to childhood trauma, when compared with non-exposed controls. Diverse types of traumatic experience impacted differently on inflammatory markers' levels: increased TNF-α and IL-6 were found associated with physical and sexual abuse, while increased CRP levels appeared to be related to parental absence during childhood [11]. Cytokines levels in FEP patients traumatized during childhood were proven to differ significantly from those of both patients without childhood trauma [33,34] and healthy controls [34]. FEP patients with childhood trauma had significantly higher serum levels of TNF-α [33] and CRP [34] when compared with patients without childhood trauma. In particular, the association between childhood trauma and CRP was found to be specific for severe sexual abuse. Specifically, patients who had experienced severe sexual abuse showed higher levels of CRP when compared with both patients without such experience and with healthy controls [34].

Epigenetic modifications/gene expression

It has been demonstrated that childhood traumatic events may interact with genetic vulnerability or shape gene expression via epigenetic mechanisms, contributing to the development of psychiatric disorders [36,37].

Several studies have looked at G × E interactions as a putative missing link between childhood trauma and the development of psychosis. Specifically, several studies have focused on the effects of single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (FKBP5) gene, finding that the A allele at two SNPs (rs4713916 and rs9296158) in the FKBP5 gene are a risk factor for psychosis in traumatized individuals [38]. Moreover, individuals who are TT homozygotes at the SNP rs1360780 in the FKBP5 gene and have been exposed to childhood trauma presented higher levels of positive psychotic experiences compared to the CC homozygotes [39]. Regarding the catechol-O-methyltransferase (COMT) gene polymorphism (Val158Met) [40], two studies found that Val/Val homozygotes had significantly higher levels of psychotic experiences after exposure to childhood trauma [41,42].

Epigenetic modifications, like cytosine residues methylation, are known to determine whether a DNA region is compacted and transcriptionally repressed/silent or open and transcriptionally active [43]; they regulate functional expression of genes by decreasing, silencing or increasing gene expression. Epigenetics, has been proven to participate in transducing environmental experiences in both genome and brain structure modifications, potentially underlining the association between childhood trauma and the development of psychosis [44]. Childhood trauma could thus influence gene expression and individuals' capacity of adaptation through epigenetic modifications [45]. Evidence concerning genome-wide methylation and gene expression modifications in FEP [46] shows a global DNA hypo-methylation in FEP patients when compared with controls [47], in line with available knowledge proving global DNA hypo-methylation in schizophrenia [48,49]. Moreover, genes related to transduction, RNA processing, lipid/glucose/protein metabolism, and mitochondrion functioning were prov-

en differently methylated or expressed in FEP patients when compared with healthy controls. In terms of gene expression profile, MPB, NDEL1, AKT1 and DICER1 were found hyper-expressed, while GCH1, DROSHA, COMT, and DISC1 resulted hypo-expressed in FEP patients in comparison with healthy controls. These genes and their proteins are all involved in a variety of CNS functions including neurodevelopment, plasticity and neurotransmission [50,51]. Such alterations could be considered both a direct (expression of a true biological difference) and an indirect (for example related to environmental exposures) manifestation of the psychosis. Childhood trauma per sé has also been proven associated to epigenetic and gene expression modifications in healthy individuals [46]. In terms of genome wide DNA methylation, genes related to central nervous system development [52,53], plasticity and degeneration [52,53], immune system and inflammatory response [53] were found differently methylated in healthy children and adolescents exposed to childhood trauma. When looking at target gene methylation related to childhood trauma in healthy subjects, SLC6A4, NR3C1, KITLG and OXTR [54] promoter regions were found hyper-methylated, while FKBP5 [55,56] and IL-6 [57,58] promoter regions and BDNF gene body [56] were demonstrated hypo-methylated in comparison to controls. Being methylation within promoter regions negatively correlated with gene expression, it is possible to speculate that childhood trauma leads to reduction in SLC6A4, NR3C1, KITLG and OXTR gene expression, favoring a dysfunctional serotonergic system (SLC6A4), an altered stress-reactivity (NR3C1, KITLG) and impaired social behavior and bonding (OXTR). In line with this hypothesis, healthy individuals with childhood trauma had reduced SLC6A4 gene expression [54], while no evidence is available demonstrating a reduction of NR3C1, KITLG or OXTR gene expression in association with childhood trauma. Given the reduced methylation within their promoter regions, it is also possible to hypothesize an increase in FKBP5 and IL-6 gene expression [59] in association with childhood trauma. Both genes encode proteins involved in the stress response system and their hyper-expression could favor a pro-inflammatory, stress-vulnerable phenotype. On the contrary, a gene is less expressed when hypomethylated in its body [60]. As mentioned above, BDNF gene was found significantly hypo-methylated within its body in healthy subjects with childhood trauma [56]; a reduced BDNF gene transcription could thus be a consequence. Despite the known impact of childhood traumatic experiences on FEP individuals [61] and the attention paid recently to epigenetics and gene expression, available studies relating to the epigenetic /gene expression modifications associated with childhood trauma in FEP patients were only three [33,62,63]. Out of them, one study investigated genome wide DNA methylation patterns, while the other two explored gene targets gene expression profile in FEP in relation to childhood trauma [33,63]. As reviewed before [46], the first study [62] indicates that childhood trauma, and specifically emotional abuse and total trauma score, entails global DNA hypo-methylation. However, as mentioned above, similar global DNA hypo-methylation has been also found in FEP patients [47] when compared with controls, not taking into account the presence of childhood trauma. This trauma-associated lower DNA methylation could have a functional relevance to gene regulation and/or be responsible for genomic instability, which has been previously observed in schizophrenia [49]. Further investigations are therefore required to elucidate whether the global hypo-methylation is to be considered as an epigenetic consequence of childhood trauma or a trait of psychosis [46]. The second study [33] found no differences in IL-1α, IL-1β, IL-6, IL-8, MCP-1, VEGF, EGF, INF-γ and TNF-α gene expression between patients with and without childhood trauma, while the third one [63] found a negative correlation between BDNF gene expression and the number of traumatic experiences. Reduced BDNF mRNA levels associated with childhood trauma in FEP [63] could result in altered neuroplasticity, since in this study FEP patients were also characterized by a smaller left hippocampal volume. However, the same study found no association between childhood trauma and BDNF gene expression in healthy controls [63]. Conversely, it was demonstrated that BDNF gene was significantly hypo-methylated within its body, and thus potentially reduced in its expression, also in healthy subjects with a history of childhood trauma [56]. Evidence on the topic appears inconsistent and it stands unclear whether the reduced BDNF gene expression is to be ascribable to a specific effect of childhood trauma per sé, independently from the presence of psychosis. Notably, there are not available replicated findings for methylation and childhood trauma neither in FEP, nor for gene expression and childhood trauma in both FEP and healthy individuals [46]. Large, well-designed case-control studies enrolling FEP subjects both with and without childhood trauma are warranted.

Metabolic dysregulation

Confirming the long-term effects of early life stress on the body, several studies [19] have linked childhood trauma to detrimental changes in physiological functions, including metabolism.

It is in fact worth mentioning that the stress system is closely interconnected with metabolism. HPA axis interacts with glucose metabolism hormones, like insulin, glucagon, gastric-inhibitor-peptide (GIP) and glucagon-like peptide-1 (GLP-1) [64] increasing the likelihood to develop metabolic dysfunctions. Insulin has an in-

hibitory activity on HPA axis, while glucagon, GIP and GLP-1 have an enhancing one, inducing the release of corticotrophin release hormone (CRH)/adrenocorticotrophic hormone (ACTH) [64]. Moreover, glucocorticoid hormones such as cortisol, stimulate gluconeogenesis and facilitate insulin-resistance, whereby chronic HPA axis activation might be at the bottom of the development of alterations in glycemic control [65]. In turn, an increase of fat mass due to glucocorticoids worsens insulin-resistance and glycemic control, triggering a vicious circle consisting of hyper-glycaemia, hyper-lipidemia and insulin-resistance [65]. The activation of the HPA axis activation may also induce alterations in the inflammatory response, which themselves could influence glucose metabolism. Individuals with schizophrenia are at higher risk of developing type 2 diabetes which is twice that of the general population [66]. Controversial results concerning insulin resistance have been reported in drug-naïve individuals with first-episode psychosis: some studies reported higher levels of insulin [67,68], insulin-resistance [67-69], increased levels of insulin-related peptides [70] as c-peptide [71] when compared to controls. In a large cohort of FEP patients recruited by our group decreased levels of glucagon and GLP-1 in compared to controls [72] have been found. Since visceral obesity can contribute to insulin resistance [73], several studies have investigated the role of appetite regulating hormones in FEP [74] reporting lower levels of leptin in drug-naïve FEP patients compared to controls. Taken together, this evidence suggests that other factors, a part from antipsychotic medications, can play a role in the metabolic alterations observed at psychosis onset. Among these, a possible role in the genesis of metabolic alterations could be covered by childhood trauma since it increases the risk for the onset of both psychosis and metabolic dysfunctions [5,75]. Individuals exposed to child sexual and physical abuse are in fact more likely to be obese or to show three or even more symptoms of metabolic syndrome when compared with non-victims [75]. Evidence suggests that individuals who reported an exposure of childhood trauma had an increased risk of the 32% to develop later in life type 2 diabetes [76] and of the 20-50% to develop obesity [77]. Furthermore, individuals with childhood trauma have decreased HDL and increased LDL levels with lower HDL/LDL ratio [78,79], higher triglyceride levels [80], reduced T3 levels and abnormal metabolism of thyroid hormones [81], and higher prevalence of metabolic syndrome [78,82] in later life. To date, evidence whether childhood trauma is involved in the development of abnormal glucose metabolism in FEP is very limited. Only two studies [83,84] have so far explored this relationship. The first one found [83] higher levels of glycated hemoglobin in FEP patients who were physically abused during childhood compared to those were not. The second one found that c-peptide and insulin levels are higher in patients exposed to childhood trauma, suggesting that hyperinsulinemia occurs early in the course of psychosis [84]. These findings underline the importance of monitoring metabolic alterations from the onset, especially in those patients who report childhood trauma, in order to carry out therapeutic interventions aimed at recovering from the negative outcomes of both hyperinsulinemia and trauma. It is still unclear to date whether markers related to glucose metabolism may be used to prevent treatment-induced weight gain in FEP patients [85].

Conclusions

Although evidence highlights a causal relation between childhood trauma and biological maladjustment in later life, the precise developmental trajectories and their temporal coincidence have not been elucidated yet[14].

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