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Research paper

The impact of childhood maltreatment on redox state: Relationship with oxidative damage and antioxidant defenses in adolescents with no psychiatric disorder

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HIGHLIGHTS

- Early-life stress (ELS) was associated with increased protein carbonylation.
- Adolescents with ELS had higher SOD levels, TRAP kinetics but reduced GPx.
- ELS was associated with imbalance in the redox state in healthy adolescents.

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ABSTRACT

Early life stress (ELS) has been associated with biological and psychosocial alterations due to developmental reprogramming. Here, we investigated whether childhood maltreatment is associated with an imbalance between the production of oxidative markers and antioxidant defenses. Thirty adolescents with no psychiatric disorder but reporting childhood maltreatment and twenty-seven adolescents with no psychiatric disorder and no history of ELS were recruited for the study. Childhood maltreatment was investigated by the Childhood Trauma Questionnaire (CTQ). Redox state was estimated by plasma levels of protein carbonylation, total thiol content (SH), superoxide dismutase (SOD), glutathione peroxidase (GPx), as well as total reactive antioxidant potential (TRAP). Childhood maltreatment was associated with oxidative stress as shown by increased protein carbonylation. Interestingly, adolescents exposed to maltreatment also displayed higher SOD levels, TRAP kinetics and reduced GPx levels when compared with adolescents who had not undergone childhood maltreatment. No significant differences were observed for SH levels. Taken together, we provide novel evidence indicating that childhood maltreatment is associated with increased oxidative stress markers in otherwise healthy adolescents.

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1. Introduction

In the past 20 years, the impact of childhood maltreatment on children's mental health has been extensively investigated. Prolonged exposure to early life stress (ELS) can alter the brain development, increasing stress-reactivity and vulnerability to depression, post-traumatic stress disorder (PTSD), drug abuse, and schizophrenia [9,15,21–23,26,27]. It has been thought that childhood maltreatment affects neurobiological development, leading to later psychological disorders [12,35]. However, the average time between child abuse exposure and the onset of mental illness is approximately 11.5 years, which means that during adolescence many victims of childhood maltreatment could be asymptomatic or sub-symptomatic, despite the brain going through significant developmental changes [38].

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Many efforts have been done to attempt to clarify how the brain reacts to ELS, but recently evidence of increased brain oxidative damage has been described following stress [34]. Oxidative stress (OS), including higher production of reactive oxygen and nitrogen species (ROS and RNS), have been extensively implicated in the progression of psychiatric disorders, due to the high vulnerability of brain to increased oxidative load [19,29,31,36]. The imbalance between the production of ROS and engagement of antioxidant defenses in favor of the first is known by oxidative stress [19]. ROS leads to damage, either directly or indirectly, of many biological structures, including lipids, proteins and DNA, causing detrimental effects at both cellular and systemic levels [19,33]. However, at moderate concentrations, ROS and RNS play an important role in physiological processes, as for example in defense against infectious agents, and cellular signaling processes [10,42].

Protein carbonylation and protein thiol modification in plasma are common indexes of oxidative damage [7,44]. Carbonyl groups are formed when protein side chains are oxidized. The accumulation of reactive carbonylated species has been linked to increased cellular toxicity, diseases and psychological stress [11]. Similarly, protein thiol groups are formed through oxidative modifications in protein cysteines and are involved in numerous biological functions [6].

Endogenous antioxidants react with ROS and RNS to protect proteins from carbonylation and thiol modification. Superoxide dismutase (SOD) catalyzes superoxide radicals ($^{\bullet}O_2-$) into oxygen and hydrogen peroxide (H_2O_2). Subsequently, peroxides and hydroxyl radicals are metabolized by glutathione peroxidase (GPx) into water and oxygen [13,18]. Therefore, an elevation in SOD/GPx ratio could result in the accumulation of H_2O_2 and H_2O_2-derived reactive species such as hydroxyl radicals. If not removed, H_2O_2 can contribute to oxidative cellular damage [18,32]. Also, the non-enzymatic antioxidant capacity can be estimated by total reactive antioxidant potential (TRAP) [14]. TRAP measure represents the global non-enzymatic antioxidant capacity of sample that includes active free radicals scavengers such as glutathione, bilirubin, alpha-tocopherol, ascorbic acid, uric acid and remaining antioxidants [5].

Here, we hypothesize that adolescents exposed to childhood abuse and neglect may have an imbalance of ROS and antioxidant defenses. To the best of our knowledge, this is the first study to investigate the association between ELS and redox dysregulation in adolescents without psychiatric conditions.

2. Methods

2.1. Participants

Thirty healthy adolescents between 13 and 17 years old with a history of childhood maltreatment (CM) were recruited by telephone from a database about CM prevalence in students from Porto Alegre, Brazil. From the same database, twenty-seven adolescents without CM history were randomly selected by invitation letters distributed to parents. History of CM was assessed through the validated Portuguese version of Childhood Trauma Questionnaire (CTQ), as reported by Grassi-Oliveira at al., a retrospective 28-item self-report instrument developed to assess childhood maltreatment experiences through 5 subscales: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse [16]. Each scale is presented in a 5-point Likert-type scale ranging from 5 (no trauma) to 25 (extreme trauma) and the total score is classified from no trauma to extreme trauma according to Bernstein et al. [4]. Briefly, severity of each of the five subscales is scored as the following; emotional abuse 13–15 = moderate to severe and over 15 = severe or extreme. Physical abuse severity up to 7 = none or minimal abuse, 8–9 = low to moderate, 10–12 = moderate to severe and over 12 = severe abuse. Sexual abuse severity up to 5 = none or minimal abuse, 6–7 = low to moderate, 8–12 = moderate to severe and over 12 = severe to extreme abuse. Emotional neglect severity up to 9–none or minimal abuse, 10–14 = low to moderate abuse, 15–17 = moderate to severe and over 17 = severe to extreme. Physical neglect severity up to 7 = none or minimal, 8–9 = low to moderate, 10–12 = moderate to severe and over 12 = severe to extreme [4,41]. Childhood Depressive Inventory (CDI) was used to evaluate depressive symptoms and severity [24]. There are 27 items and each item scored on a three-point scale: 0 = absent; 1 = moderate; 2 = severe, classified in order of increasing severity from 0 to 2, which ranges from 0 to 54. A cut-off up to 20 scores indicates the absence of depressive symptoms. Exclusion criteria to both groups were: (a) presence of major axis I disorder such as psychotic disorders, mood disorders, anxiety disorders as well as trauma-related disorders, (b) mental retardation, (c) presence of systemic (hypertension, immune disorders or infection) or neurological diseases, (d) neoplasias, and (e) use of any substance that may induce immune or endocrine changes. Exclusion criteria were determined by interviews and by the *Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime Version* (K-SADS-PL) and the *Wechsler Abbreviated Scale of Intelligence* (WASI) inventories [3,43]. This study was approved by the Ethical Committee of Pontifical Catholic University of Rio Grande do Sul (PUCRS), and all subjects provided their written informed consent before inclusion in the study.

2.2. Blood collection and plasma isolation

Ten milliliters of peripheral blood were collected by venipuncture and stored in EDTA tubes prior to analyses. Immediately after blood collection, the samples were centrifuged at 1800 rpm for 5 min and the plasma samples were stored at −80 °C until analysis.

2.3. Protein carbonylation

Oxidative damage to proteins was measured by quantification of carbonyl groups as previously described [47]. This method is based on the reaction of dinitrophenylhydrazine (DNPH) with protein carbonyl groups. Briefly, proteins were precipitated by the addition of 20% TCA and re-solubilized in DNPH, and absorbance determined by spectrophotometer at 370 nm. Results are expressed in μmol carbonyls/mg protein.

2.4. Protein thiol content

In order to measure the levels of reduced thiol (-SH) groups in protein in serum samples we used the Ellman's reagent based assay [46]. For this, 60 μg sample aliquot was diluted in PBS followed by the addition of 0.01 M 5,5-dithiobis-2-nitrobenzoic acid (DTNB). After 60 min incubation at room temperature, the absorbance was measured in a spectrophotometer set at 412 nm. Results are expressed as μmol SH groups/mg protein.

2.5. Antioxidant enzymes activity quantification

Superoxide dismutase (SOD) activity was estimated from the inhibition of superoxide anion-dependent adrenaline autoxidation in a spectrophotometer at 480 nm as previously described [50]. Results were expressed as units of SOD/mg protein. Moreover, GPx activity was measured in plasma samples by the rate of NAD(P)H oxidation accessed in a spectrophotometer at 340 nm in the presence of reduced glutathione, tert-butyl hydroperoxide, and glutathione reductase as previously described [51].

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