

Inflammation in children with ADHD: from HPA axis, Inflammatory biomarkers to neurotrophins

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Background

Several stress-relevant biological systems have possible roles in attention deficit hyperactivity disorder (ADHD), including the hypothalamic-Pituitary-Adrenal (HPA) axis and cortisol levels, inflammation and neurotrophins. Previous literature reported lower cortisol levels in children with ADHD, but other studies did not report such differences between ADHD and typically developing youths (TD). In addition, there have been little study on the inflammation biomarkers and neurotrophins in children with ADHD.

Aims & Objectives

The aim is to investigate HPA axis, inflammation and neurotrophins in children with ADHD.

Methods

First, we conducted a case-control study measuring saliva cortisol levels at 4 different time points during the day (at awakening, noon, 1800 h and bedtime) and morning plasma levels of inflammatory and neurotrophins biomarkers in youth with ADHD ($n = 98$, age 6–18 years old with mean age 9.32 ± 3.05 years) and TD ($n = 21$, age 6–18 years old with mean age 9.19 ± 2.96 years) in Taiwan. Second, we conducted a systematic review followed by a meta-analysis of case-control studies assessing blood or saliva cortisol levels and blood levels of inflammatory biomarkers in youth with ADHD. The effect sizes (ES) were synthesized by using a random-effects model. We included 19 studies in the meta-analysis on cortisol levels (totaling $n = 916$ youth with ADHD and $n = 947$ TD) and 4 studies (totaling $n = 404$ youth) in the meta-analysis on inflammation biomarkers.

Results

Our study showed that youth with ADHD have lower levels of bedtime salivary cortisol ($p = .023$), with children with the combined form of the disorder (with inattention, hyperactivity and impulsivity all present) having the lowest awakening salivary cortisol levels. ADHD youth also have higher levels of plasma high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6 ($p < 0.0001$), and lower plasma tumor necrosis factor-alpha (TNF- α) ($p = 0.009$) and brain-derived neurotrophic factors (BDNF) ($p < 0.0001$). The meta-analysis also showed youth with ADHD have lower basal cortisol levels at any time-points during the day (ES: .68, $p = 0.004$) and lower cumulative levels of cortisol (ES: .39, $p = 0.008$) throughout the day than TD youth. The meta-analysis on inflammation biomarkers showed that TNF- α is lower in ADHD when compared with TD ($p = 0.004$).

Discussion & Conclusion

The lower salivary cortisol levels and abnormal levels of inflammatory biomarkers in youth with ADHD further support the role of abnormal HPA axis and inflammation in ADHD. Moreover, the lower levels of BDNF in ADHD also indicate that BDNF may be a potential biomarker in this disorder that is part of a broader biological dysfunction.