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Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents

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ABSTRACT

An adverse early life environment can induce changes on behavioral and metabolic responses later in life. Recent studies in rats showed that the quality of maternal care as measured by high levels of pup licking and grooming (LG) was associated with changes in the relationship between the precursor thyroid-hormone T4 and the more active T3. Here we investigated if early exposure to childhood abuse is associated with thyroid-hormone levels in human adolescents. Given the empirical evidence from animal models showing that good maternal care was associated with increased conversion of T4 to T3, we hypothesized that early adversity would be associated with a decreased peripheral conversion of T4 to T3. A sample of 80 adolescents (10–18 years) participated in this study. We used the Childhood Trauma Questionnaire to investigate early life stress. We calculate the body mass index (BMI) assessing weight and height and sexual maturation stage was determined by self-assessment. Blood samples were collected to measure T3 and T4 levels. ANCOVA were used to evaluate the influence of the Physical Abuse domain of the Childhood Trauma Questionnaire as the early life stress variable in T3 and T4 separately, adjusted for potential confounders such as pubertal status, gender, socioeconomic status and BMI. Early life trauma was associated with reduced T3 levels in adolescents, when adjusted for potential confounders ($p = 0.013$), but not with peripheral T4 levels ($p = 0.625$). We extended findings from animal models showing that adverse early experience persistently impacts on the individual's responses to stress, which is marked by an abnormal metabolism of thyroid hormones. Further studies are needed to further investigate the nature of such associations.

1. Introduction

Early life stress (ELS) has shown to have profound impacts on health throughout the lifespan (Alastalo et al., 2013; Etter et al., 2013; MacMillan et al., 2001) and it can induce changes on behavioral and metabolic responses later in life (Pervanidou and Chrousos, 2012). Studies have shown that ELS is associated with depression, personality disorders (Sudbrack et al., 2015; Weber et al., 2008), temperament traits (Sudbrack et al., 2015), anxiety, drug addiction and antisocial behavior in adulthood (MacMillan et al., 2001) as well as a variety of other medical problems (Fergusson et al., 2008; Spitzer et al., 2013). Among the different types of trauma, physical abuse is consistently associated with poor outcomes (Bailer et al., 2014; Bailey et al., 2012; Fuller-Thomson and Hooper, 2015; Petrenko et al., 2012; Schneiderman et al., 2014). Despite that, the mechanistic links between ELS and poor health are still poorly understood.

One prominent hypothesis is that stress early in life may cause persistent programming changes on the hypothalamic–pituitary–adrenal (HPA) axis functioning. The HPA activation culminates with glucocorticoid release, being

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highly adaptive for survival in facing an acute stress situation. However, chronic/persistent hyperactivation of this axis can cause damage (Herman et al., 2003). ELS such as maltreatment (physical, sexual or emotional abuse and neglect) may persistently enhance the HPA activity (Mello et al., 2009; Trickett et al., 2010) and evidences from experimental studies propose a hyper-reactivity of HPA axis in adulthood caused by ELS (Machado et al., 2013).

In animal models, it was shown that the poor quality of maternal care, as measured by low levels of pup licking and grooming (LG) over the first week of life, decreases hippocampal glucocorticoid receptor (GR) expression, diminishes glucocorticoid feedback sensitivity over hypothalamic corticotrophin-releasing factor (CRF) synthesis and leads to more exuberant adrenal glucocorticoid responses to stress in comparison with those reared by High-LG mothers (Francis et al., 1999; Liu et al., 1997; Toki et al., 2007; van Hasselt et al., 2012; Weaver et al., 2004, 2005). A broad range of in vivo and in vitro studies demonstrates that pup LG increases GR gene transcription in the offspring through epigenetic mechanisms, specifically through effects on DNA methylation in the exon 1_7 GR promoter. This is suggested to occur in response to an increase in NGFIA as a consequence of a thyroid-hormone-dependent increase in 5-HT activity at 5-HT7 receptors and the subsequent activation of cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase A (PKA) (Champagne et al., 2003; Laplante et al., 2002; Meaney et al., 1987, 2000; Mitchell et al., 1992, 1990a,b; Weaver et al., 2007). Previous experimental studies implicate thyroid hormones in the regulation of hippocampal 5-HT activity and GR expression (Meaney et al., 1987, 2000), and it was recently demonstrated that an increased frequency of pup LG in rats associates with an increased conversion of the T4 precursor to the more active T3 (Hellstrom et al., 2012). Therefore, maternal care regulates GR expression through increases in hippocampal 5-HT that lie downstream of the dynamic T3 signaling. In humans, similarly to pup LG, maternal stroking in infancy is able to modify the effect of maternal prenatal depression on infant reactivity (Sharp et al., 2012). More specifically, low maternal stroking in those women that had prenatal depression is related to increased infant negative emotionality and decreased physiological adaptability (Sharp et al., 2012). It is described decreased levels of glucocorticoid receptor mRNA, as well as mRNA transcripts bearing the glucocorticoid receptor 1F splice variant in human hippocampal samples from suicide victims with a history of childhood abuse (McGowan et al., 2009). This suggests that the effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression also happens in humans. Despite that, the effects of early life stress on thyroid hormones metabolism are not well known. The objective of our study was to investigate whether changes in thyroid hormone metabolism could be good candidates to explain mechanistic links between early life stress and negative health outcomes. Here, we hypothesize that exposure to childhood abuse (specifically physical abuse) could predict abnormal thyroid-hormone metabolism later in life, being related to decreased peripheral conversion of T4 to T3 as seen in the animal model (pups reared by Low-LG mothers). Recent studies show that among the different types of trauma, the adverse consequences of childhood physical abuse persist in different systems, affecting the inflammatory response, cardiovascular function, lipid metabolism (Friedman et al., 2015), obesity risk (Francis et al., 2015) and even telomere length (Mason et al., 2015). Therefore, we focused on this specific type of trauma for its long-term consequences on physical health.

Table 1
Characteristics distribution of the subjects for T3 and T4.

	T3				T4			
	N	Mean	SD	*p*-Value	*N*	Mean	SD	*p*-Value
CTQ-physical abuse score				0.004**				0.539**
Low	44	152.3[a]	30.38		44	9.6	1.50	
Intermediate	10	158.7[a]	27.95		10	9.3	1.27	
High	26	130.4[b]	24.75		26	9.9	1.32	
Pubertal status				0.002**				0.127**
Pre-puberty	14	159.7[a]	28.31		14	10.0	1.06	
Puberty	31	154.2[a]	28.67		31	9.3	1.51	
Post-puberty	35	133.2[b]	27.77		35	9.9	1.39	
Gender				0.292*				0.931*
Male	29	150.7	27.71		45	9.7	1.25	
Female	51	143.3	31.36		86	9.7	1.50	
Socioeconomic status				0.036*				0.512*
Low	24	135.2	28.53		24	9.8	1.56	
High	56	150.6	29.85		56	9.6	1.35	
BMI	80	$r = 0.246$		0.028#	80	$r = 0.270$		0.015#

Data presented as mean ± SD.
* *p* Value for Student's *t* test.
** *p* Value for one-way analysis of variance (ANOVA), means followed by the same letter are not significantly different by Bonferroni test.
\# *p* Value for pearson's correlation.

2. Materials and methods

2.1. Participants

The current study addressed a sample of 80 students between 10 and 18 years old (63.8% female; mean age 13.6 years, SD = 2.44) that were evaluated at school. Detailed description of the sample selection can be found elsewhere (Salum et al., 2011). The objective of this study was to investigate anxiety disorders and therefore, anxiety cases were privileged, so that the sample included all children classified in the upper quartile of the SCARED instrument

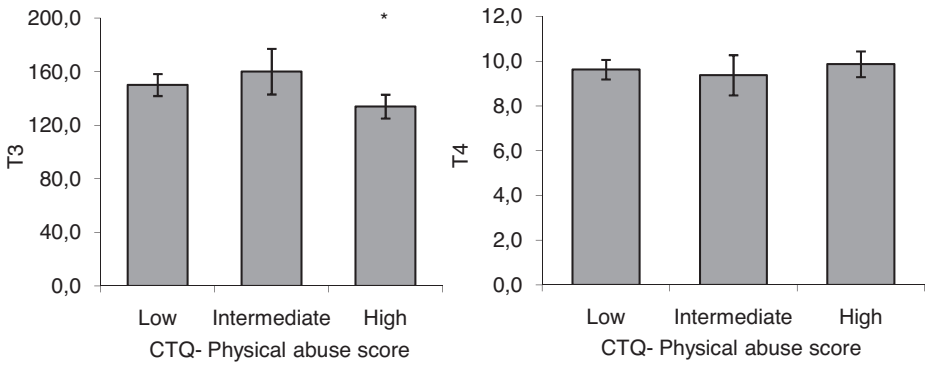

Fig. 1. Adjusted mean and CI-95% for T3 and T4 according to CTQ- Physical abuse score. * ANCOVA adjusted for pubertal status, gender, socioeconomic status and BMI, $p < 0.05$.