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Psychosocial stress and inflammation driving tryptophan breakdown in children and adolescents: A cross-sectional analysis of two cohorts

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ABSTRACT

Background: Tryptophan breakdown is an important mechanism in several diseases e.g. inflammation and stress-induced inflammation have been associated with the development of depression via enhanced tryptophan breakdown. Depression is a major public health problem which commonly starts during adolescence, thus identifying underlying mechanisms during early life is crucial in prevention. The aim of this work was to verify whether independent and interacting associations of psychosocial stress and inflammation on tryptophan breakdown already exist in children and adolescents as a vulnerable age group.

Methods: Two cross-sectional population-based samples of children/adolescents (8–18 y) were available: 315 from the European HELENA study and 164 from the Belgian ChiBS study. In fasting serum samples, tryptophan, kynurenine, kynurenic acid, C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-α, interferon (IFN)-ɣ, soluble vascular adhesion molecule 1 (sVCAM1) and soluble intercellular adhesion molecule 1 (sICAM1) were measured. Psychological stress was measured by stress reports (subjective) and cortisol (objective – awakening salivary cortisol or hair cortisol). Linear regressions with stress or inflammation as predictor were adjusted for age, sex, body mass index, puberty, socio-economic status and country.

Results: In both cohorts, inflammation as measured by higher levels of CRP, sVCAM1 and sICAM1 was associated with kynurenine/tryptophan ratio and thus enhanced tryptophan breakdown (beta: 0.145–0.429). Psychological stress was only associated with tryptophan breakdown in the presence of higher inflammatory levels (TNF-α in both populations).

Conclusions: Inflammatory levels were replicable key in enhancing tryptophan breakdown along the kynurenine pathway, even at young age and in a non-clinical sample. The stress-inflammation interaction indicated that only the stress exposures inducing higher inflammatory levels (or in an already existing inflammatory status) were associated with more tryptophan breakdown. This data further contributes to our understanding of pathways to disease development, and may help identifying those more likely to develop stress or inflammation-related illnesses.

1. Introduction

The tryptophan-kynurenine pathway which catabolizes 95% of tryptophan, has been linked to several diseases like psychological disorders, impaired cognition and cardiometabolic diseases (O'Farrell and Harkin, 2017; Oxenkrug, 2010a). In this tryptophan-to-kynurenine breakdown (Fig. 1), two enzymes have a leading role: indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO) (Oxenkrug, 2010b). IDO1 activity is mainly induced by pro-inflammatory molecules such as interferon (IFN)-ɣ, IFN-α and tumor necrosis factor (TNF)-α as IDO1 is widely expressed on immune cells like dendritic cells, macrophages, microglia and eosinophils (Takikawa et al., 1999). TDO is

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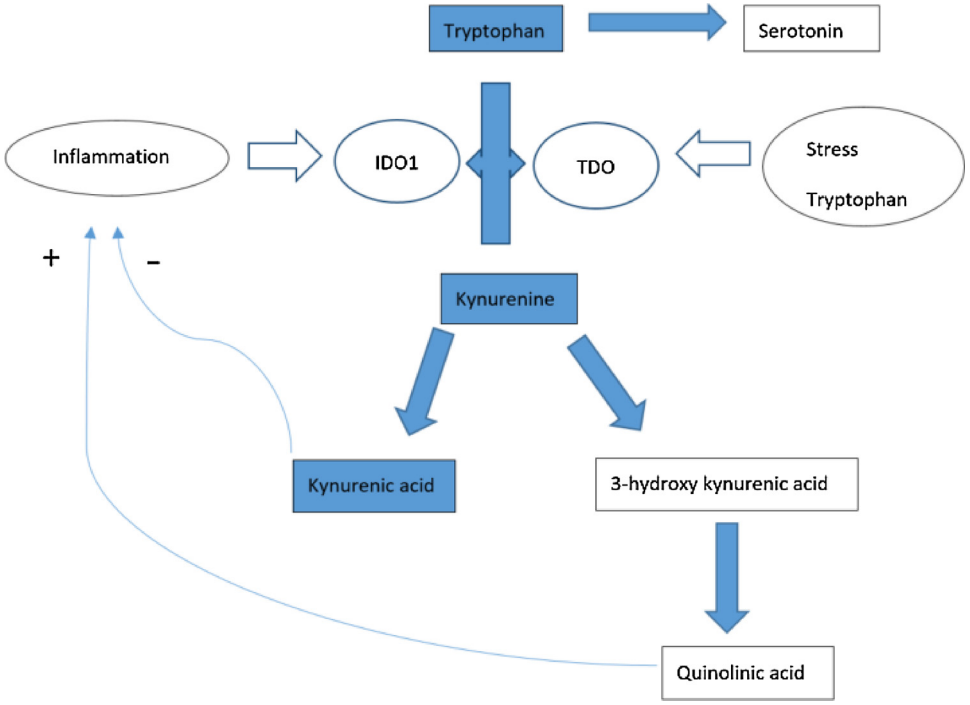

Fig. 1. The tryptophan breakdown pathway. TDO = tryptophan 2,3-dioxygenase, IDO = indoleamine 2,3-dioxygenase. Metabolites in the blue boxes were measured in the current study. Interesting, some metabolites of kynurenine like kynurenic acid are anti-inflammatory and neuroprotective, while others like quinolinic acid are pro-inflammatory and neurotoxic.

involved in the negative feedback i.e. high tryptophan will stimulate tryptophan breakdown via TDO activation, but also stress, mainly via the stress hormone cortisol, can induce TDO activity (Gibney et al., 2014). The IDO1 and TDO stimulated conversion of tryptophan to kynurenine will also lead to diminished serotonin production as tryptophan is a precursor of serotonin (Oxenkrug, 2010b). The resulting kynurenine can largely be metabolised via two pathways (Oxenkrug, 2010b; Schwarcz et al., 2012) (Fig. 1): (1) via the formation of kynurenic acid as a neuroprotective and anti-inflammatory metabolite or (2) via the predominantly neurotoxic and pro-inflammatory quinolinic acid branch because of *N*-methyl-D-aspartate receptor stimulation, lipid peroxidation and disruption of the blood-brain barrier (although also functional metabolites like NAD arise in this branch). Consequently, the kynurenine/tryptophan ratio reflects the first step of tryptophan breakdown by TDO or IDO, while the kynurenic acid/kynurenine ratio can reflect a next step away from the pro-inflammatory tryptophan metabolites.

It has now become apparent that this tryptophan-to-kynurenine breakdown contributes to the development of age-associated neuroendocrine disorders (hypertension, dyslipidaemia, type 2 diabetes, obesity, vascular cognitive impairment and some hormone-related cancers) and mood disorders (O'Farrell and Harkin, 2017; Oxenkrug, 2010a). Partially this is because of apoptotic, neurotoxic, and pro-oxidative effects of certain tryptophan metabolites like quinolinic acid; partially this is because of diminished serotonin production which is linked to mood, sleep, sexual behaviour, cognition and appetite (Hulsken et al., 2013; O'Farrell and Harkin, 2017; Oxenkrug, 2010a).

Because of IDO and TDO activity, inflammation and stress may be two pathological situations affecting tryptophan breakdown and can converge to have further health deteriorating results via this mutual pathophysiological process, especially when an optimal supply of tryptophan and its metabolites to the central nervous system is desirable. Of particular interest is the increasing amount of evidence that inflammation and chronic stress might stimulate each other via interaction between cytokines and cortisol (Hansel et al., 2010; Leonard, 2005). Nevertheless, only a few studies exist on the role of inflammation (cytokines and related molecules like acute phase proteins and cell-adhesion molecules) and stress in the tryptophan breakdown using an overall population sample (Deac et al., 2016; Elovainio et al., 2012; Pertovaara et al., 2007) and none in children. Research has often focused on patients with depression showing higher tryptophan breakdown (Maes et al., 1993; Myint et al., 2013), but not in everyone (Gabbay et al., 2010). Concerning inflammation, IFN-γ is known as the strongest inducer of IDO1, although this association is not always evident in healthy populations (Deac et al., 2016; Fitzgerald et al., 2008). Thus, a better understanding of the role of tryptophan breakdown following psychosocial stress and inflammation during vulnerable periods like childhood and adolescence, and hence early in the disease process, is necessary.

The goal of the current paper is to examine whether the association of inflammation and stress with tryptophan metabolites could be already observed in children and adolescents. This is important as tryptophan breakdown could then potentially be used as early target for prevention. To allow replication, the independent and interacting associations of psychosocial stress (subjectively and objectively measured) and inflammation (six markers) on enhanced tryptophan breakdown was tested in two population samples of children and adolescents.

2. Methods

2.1. Study samples

Two population samples of children/adolescents have been used.

The HELENA-Cross Sectional Study was conducted in 3528 adolescents aged 12.5–17.5 from 10 European cities from 2006 to 2007. Details on sampling procedures and study design of the HELENA study have been reported elsewhere (Moreno et al., 2008). For this paper, specific inclusion criteria were the availability of serum (and thus tryptophan and inflammation data) and the stress questionnaire (which was an optional module) and the absence of an acute infection (CRP > 10 mg/l) as was the case in 315 adolescents. Included participants seemed to have a lower BMI than those with missing data (z-score 0.2 vs 0.5), but did not differ in sex or age. Only in a subsample (n = 161, from the same six countries), salivary cortisol was available; this sample did not differ in BMI or sex but was somewhat younger (mean age 14.3 vs 14.8 y, but same age range) than the other 155 included participants.