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Circulating tumour necrosis factor is highly correlated with brainstem serotonin transporter availability in humans

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ABSTRACT

Preclinical studies demonstrate that pro-inflammatory cytokines increase serotonin transporter availability and function, leading to depressive symptoms in rodent models. Herein we investigate associations between circulating inflammatory markers and brainstem serotonin transporter (5-HTT) availability in humans. We hypothesised that higher circulating inflammatory cytokine concentrations, particularly of tumour necrosis factor (TNF-α), would be associated with greater 5-HTT availability, and that TNF-α inhibition with etanercept (sTNFR:Fc) would in turn reduce 5-HTT availability. In 13 neurologically healthy adult women, plasma TNF-α correlated significantly with 5-HTT availability (rho = 0.6; $p = 0.03$) determined by [^{123}I]-beta-CIT SPECT scanning. This association was replicated in an independent sample of 12 patients with psoriasis/psoriatic arthritis (rho = 0.76; $p = 0.003$). Indirect effects analysis, showed that there was a significant overlap in the variance explained by 5-HTT availability and TNF-α concentrations on BDI scores. Treatment with etanercept for 6–8 weeks was associated with a significant reduction in 5-HTT availability ($Z = 2.09$; $p = 0.03$; $r = 0.6$) consistent with a functional link. Our findings confirm an association between TNF-α and 5-HTT in both the basal physiological and pathological condition. Modulation of both TNF-α and 5-HTT by etanercept indicate the presence of a mechanistic pathway whereby circulating inflammatory cytokines are related to central nervous system substrates underlying major depression.

1. Introduction

Studies over the last few decades have found a strong link between inflammatory processes and psychiatric illnesses, particularly major depressive disorder (MDD). At least three meta-analyses have confirmed the presence of greater circulating inflammatory marker levels in major depressive disorder (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012). Greater circulating inflammatory marker levels have been found to predict the development of MDD in longitudinal studies (Valkanova et al., 2013). Among medically ill, those with inflammatory diseases are at greater risk of developing a major depressive illness (Kurd et al., 2010).

While the above findings are essentially correlational, a causal link has been proposed by findings that patients treated with cytokines for illnesses like hepatitis C, are at greater risk of developing a major depressive illness (Loftis et al., 2013; Myint et al., 2009). Conversely, biological anti-inflammatory agents, that target proinflammatory cytokines in a highly specific manner, induce an antidepressant effect in patients, independent of improvement in the inflammatory condition (Feldmann and Maini, 2001, 2003, 2010; Feldmann et al., 2010; Tyring et al., 2006). Given these clinical observations, it is proposed that the immune system and inflammation may play a role in the aetiopathogenesis of MDD (Dantzer et al., 2008; Kelley et al., 2003; Krishnadas and Cavanagh, 2012; Raison et al., 2006; Smith, 1991; Stein et al., 1991).

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When exploring the pathophysiological underpinnings of depression, the monoamine neurotransmitter systems remain a central and translationally relevant biological substrate (Schildkraut, 1965).

Among the monoamines, the serotonergic system modulates emotional regulation, reward and punishment processing, behavioural inhibition, delay discounting and has been implicated in the aetiopathogenesis of MDD (Cools et al., 2008; Massart et al., 2012; Schildkraut, 1965) [see (Albert and Benkelfat, 2013; Albert et al., 2012) for a special issue on an update on the serotonin hypothesis in the neurobiology of depression]. The mesencephalic rostral raphe nuclei (including the median and dorsal raphe) account for 85% of all serotonergic neurons in the brain. They innervate the cerebral cortex and the limbic forebrain, including the hypothalamus, hippocampus and amygdala and receive descending projections from the limbic forebrain and ascending projections from the periaqueductal grey matter (Descarries et al., 2010). The serotonin transporter (5-HTT) plays an essential role in serotonin neurotransmission, by regulating synaptic serotonin levels. They are not only present in the projection areas on the neuronal presynaptic cell membrane, but also on cell bodies within the raphe nuclei distributed near the midline of the brainstem (Canli and Lesch, 2007; Descarries et al., 2010; Hornung, 2003; Maximino, 2012). In vitro studies confirm a significant correlation between 5-HTT levels and tissue concentrations of serotonin, suggesting that the former is a proxy marker for serotonin in healthy brain (Dewar et al., 1991). Depressive symptoms in humans have been associated with increased availability/function of 5-HTT, pointing to a reduction in synaptic serotonin levels (Meyer, 2008; Savitz and Drevets, 2013). While the monoamine hypothesis by itself is far from complete in explaining the pathophysiology underlying depression, a majority of available antidepressants inhibit 5-HTT at therapeutic doses and promote an increase in synaptic serotonin (Meyer, 2012).

The serotonergic neurotransmitter system is a prime candidate to explore the link between inflammation and the aetiopathogenesis of MDD. This potential link is supported by findings from preclinical studies in rodent models that directly link proinflammatory cytokines with brain 5-HTT availability through activation of MAPK pathways (Baganz and Blakely, 2013; Couch et al., 2013; Katafuchi et al., 2006; Malynn et al., 2013; Morikawa et al., 1998; Ramamoorthy et al., 1995; Samuvel, 2005; Tsao et al., 2008). There are number of pathways through which circulating inflammatory markers can signal the brain including active transport across the blood-brain barrier (BBB); second messenger signals from the endothelial lining of BBB; through afferent vagal pathways; passage of cytokines through 'leaky' regions in the BBB (Capuron and Miller, 2011). Of particular theoretical relevance is that, in humans, the raphe nuclei (dorsal) are located close to the cerebral aqueduct making it particularly vulnerable to inflammatory signalling molecules present in the cerebral spinal fluid (CSF) (Howerton et al., 2014). They are also highly connected with humoral sensing circumventricular organs like the subfornical organ, which have fenestrated capillaries that allow exposure to large molecules like inflammatory cytokines, and form part of the key viscerosensory paths in the brain (Critchley and Harrison, 2013; Wallacelind, 1986).

No human studies have examined the association between circulating inflammatory markers and brainstem 5-HTT availability. Herein, we addressed two key questions. Firstly, is there a relationship between circulating inflammatory markers and 5-HTT in humans? And secondly, will highly specific cytokine inhibition result in changes in 5-HTT availability? Thus, we explored the association between circulating inflammatory markers and brainstem 5-HTT availability in a cohort of neurologically healthy volunteers and replicated our finding in a cohort of patients with psoriasis/psoriatic arthritis. We also ascertained whether administration of etanercept (TNF receptor:Fc fusion protein) would be associated with changes in serotonin transporter availability. In keeping with preclinical studies, we hypothesised that greater pro-inflammatory cytokine concentrations would be associated with greater 5-HTT availability in the brain, and that treatment with etanercept would be associated with a reduction in 5-HTT availability.

2. Materials and methods

2.1. Study design

The study was approved by the West of Scotland Research ethics committee and the Administration of Radioactive Substances Advisory Committee. All participants gave written informed consent. The study was conducted on two independent groups of subjects.

2.2. Healthy subjects

Firstly, we explored the association between, circulating inflammatory markers and brainstem 5-HTT availability in a group of healthy adult subjects (Fig. 1a). Circulating inflammatory marker concentrations and 5-HTT availability data were obtained from thirteen healthy menopausal women who were non-smokers, non-hypertensive, non-diabetic and not taking any drugs which could affect vascular function, and not being prescribed antidepressant medications or hormone replacement treatment. Data from this sample exploring a different hypothesis has been published previously as part of another study (Sassarini et al., 2014).

2.3. Psoriasis/psoriatic arthritis subjects

We then replicated this association in a group of patients with psoriasis/psoriatic arthritis. Fifteen subjects diagnosed with psoriasis/psoriatic arthritis aged 30–65 years, were recruited into the study. Three patients dropped out – one withdrew consent, and the other two had incidental findings on the MRI. Therefore, data from 12 individuals were analysed. All patients met disease activity criteria set by NICE pertaining to the use of Etanercept for psoriasis and psoriatic arthritis, and had been previously treated with a disease modifying agent (methotrexate) for at least 6–8 weeks. Those who incidentally fulfilled the criteria for MDD were included in the study. However, those with a history of antidepressant intake in the previous 3 months; history of cerebrovascular disease, documented head trauma or neurological disorders, lifetime history of DSM Axis I psychiatric diagnoses other than depression (measured using SCID), alcohol and/or substance misuse, pregnancy, other connective tissue or systemic inflammatory disease were excluded from participation. None of the patients fulfilled a SCID diagnosis for a DSM IV Axis 1 psychiatric disorder, and none of them were started on an antidepressant during the study.

Finally, in order to examine if highly specific TNF inhibition would alter 5-HTT availability, we compared 5-HTT availability, before and after treatment with etanercept for 6–8 weeks (Fig. 1b). Etanercept is a recombinant human TNF-α receptor fusion protein with 934 aminoacids and weighs 150 kDa (Strober et al., 2008; Tan et al., 2007). It binds to TNF-α, thereby blocking its interaction with cell-surface receptors (Feldmann and Maini, 2001, 2010). Etanercept is licensed for use in adults with active psoriasis/psoriatic arthritis (Fantuzzi et al., 2008). The administration of etanercept provided a molecular scalpel to interrogate the functional implications of the elevated TNF levels (and consequent inflammation) present in patients with psoriasis/psoriatic arthritis.