Psychoneuroendocrinology 62 (2015) 80–88

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

An inverse relationship between serum macrophage inhibitory cytokine-1 levels and brain white matter integrity in community-dwelling older individuals

Jiyang Jiang[a], Julian N. Trollor[a,b], David A. Brown[c], John D. Crawford[a], Anbupalam Thalamuthu[a], Evelyn Smith[a], Samuel N. Breit[c], Tao Liu[d], Henry Brodaty[a,e,f], Bernhard T. Baune[g], Perminder S. Sachdev[a,h], Wei Wen[a,h,*]

[a] Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Randwick, NSW, Australia
[b] Department of Development Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
[c] Centre for Applied Medical Research, St. Vincent's Hospital and University of New South Wales, Darlinghurst, NSW, Australia
[d] School of Biological Science and Medical Engineering, Beihang University, Beijing, China
[e] Aged Care Psychiatry, Prince of Wales Hospital, Randwick, NSW, Australia
[f] Dementia Collaborative Research Centre, University of New South Wales, Sydney, NSW, Australia
[g] Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia
[h] Neuropsychiatric Institute, Prince of Wales Hospital, Randwick, NSW, Australia

ARTICLE INFO

Article history:
Received 13 March 2015
Received in revised form 17 July 2015
Accepted 23 July 2015

Keywords:
Macrophage inhibitory cytokine-1
White matter integrity
Community-dwelling
Ageing
Magnetic resonance imaging

ABSTRACT

Macrophage inhibitory cytokine-1 (MIC-1/GDF15) is a marker of inflammation that has been associated with atherosclerosis. We have previously demonstrated its relationships with cognitive decline and cerebral gray matter volumes, suggesting its role as a biomarker of cognitive impairment. Considering that it is widely distributed in the brain, and both inflammation and vascular pathology impact on white matter (WM) integrity, we examined the relationship between MIC-1/GDF15 and measures of WM integrity, including WM volumes, mean fractional anisotropy (FA) values and WM hyperintensity (WMH) volumes in a community-dwelling non-demented sample of older individuals ($n = 327$, 70–90 years old). We found that the mean FA values were negatively associated with MIC-1/GDF15 serum levels, after Bonferroni correction. The voxel-wise analysis showed negative relationships between MIC-1/GDF15 serum levels and FA values in corticospinal tract, corpus callosum (including genu, body and splenium parts), superior longitudinal fasciculus, cingulum, as well as anterior and posterior thalamic radiation. Whole brain WMH volumes, especially deep WMH volumes, showed a non-significant trend for a positive association with MIC-1/GDF15 serum levels. The associations between MIC-1/GDF15 serum levels and WM integrity showed a non-significant trend of being stronger for the individuals classified as mild cognitive impairment, compared to the normal ageing participants. The findings suggest that high serum MIC-1/GDF15 levels indicate reduced WM integrity and possibly greater WM pathology.

1. Introduction

Macrophage inhibitory cytokine-1 (MIC-1/GDF15) is a divergent member of transforming growth factor-β (TGF-β) superfamily (Bootcov et al., 1997; Breit et al., 2011). As a product triggered by activated macrophages, MIC-1/GDF15 is considered to be involved in chronic inflammatory processes (Breit et al., 2011). Unlike most other inflammatory cytokines regulated by the transcription factor Nuclear Factor kappa B (NFκB) (Alberti et al., 2012; Profita et al., 2008), the expression of MIC-1/GDF15 is mainly induced by alternate transcription factors including p53 (Baek et al., 2002) and Egr-1 (Baek et al., 2005), suggesting that MIC-1/GDF15 serum levels may reflect cellular activities not sampled by commonly studied inflammatory cytokines. Blood MIC-1/GDF15 level is elevated during states such as injury (Schober et al., 2001), malignancy (Brown et al., 2009, 2006, 2003), and inflammation (Brown et al., 2007; Fairlie et al., 1999). In human without any disease process, serum

* Corresponding author at: Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Randwick 2031, NSW, Australia. Fax: +61 2 9382 3774.
E-mail address: w.wen@unsw.edu.au (W. Wen).

http://dx.doi.org/10.1016/j.psyneuen.2015.07.610
0306-4530/

MIC-1/GDF15 levels remain relatively stable, and slowly elevate with age (Brown et al., 2006).

Previous findings suggested that MIC-1/GDF15 may be anti-inflammatory (Breit et al., 2011). The expression of MIC-1/GDF15 in response to secreted pro-inflammatory cytokines tends to inhibit the later phases of macrophage activation (Bootcov et al., 1997). In animal studies, transgenic mice with overexpression of MIC-1/GDF15 had less atherosclerotic lesions after six months of high fat diet (Johnen et al., 2012). Life-long overexpression of human MIC-1/GDF15 in mice leads to alteration of key metabolic pathways and prolongation of life (Wang et al., 2014). Moreover, MIC-1/GDF15 is a potent protective factor for iron-intoxicated dopaminergic neurons cultured from the embryonic rat midbrain floor, and prevents 6-hydroxydopamine (6-OHDA)-induced neuron damage (Strelau et al., 2000).

In animal models, MIC-1/GDF15 mRNA and protein are widely detectable in the central and peripheral nervous systems from fetal development to adulthood (Schober et al., 2001; Strelau et al., 2000). Within the adult rat brain, MIC-1/GDF15 mRNA and protein is detected in a variety of regions, including cortex, hippocampus, striatum, pons, and medulla oblongata, and the protective effects of MIC-1/GDF15 on 6-OHDA-induced dopaminergic neuron loss lasted for at least one month (Strelau et al., 2000). Therefore, it is plausible that MIC-1/GDF15 has a long-term impact on brain structures.

As a novel cytokine, however, MIC-1/GDF15 has not been extensively investigated for its associations with human brains using magnetic resonance imaging (MRI), especially with WM. A recent study from our group uncovered the inverse relationship of MIC-1/GDF15 serum levels with cognitive functions (Fuchs et al., 2013) which closely correlate with WM integrity (Laukka et al., 2013). WM-related vascular disorders, such as atherosclerosis (Grinberg and Thal, 2010), were also found to be associated with MIC-1/GDF15 (Johnen et al., 2012). These findings led us to investigate the associations of serum MIC-1/GDF15 levels with WM integrity.

In healthy ageing cohorts, serum/plasma levels of some well-studied inflammatory markers, such as interleukin-6 (IL-6) (Bettcher et al., 2014; Satizabal et al., 2012) and C-reactive protein (CRP) (Taki et al., 2012; Wersching et al., 2010), have been linked to brain structural properties, such as GM/WM volumes and integrity. However, direct evidences of the relationships between these inflammatory markers and brain structures in individuals with neurodegenerative disorders are limited (Frodl and Amico, 2014). As the intermediate stage between normal ageing and dementia, mild cognitive impairment (MCI) showed dementia-like brain atrophy but to a less severe extent (Jiang et al., 2014). Since MIC-1/GDF15 serum levels are clearly elevated in disease status, it is also interesting to examine the differences in the relationships between MIC-1/GDF15 and WM integrity between cognitively normal participants (CN) and those with MCI.

Moreover, since both circulating inflammatory biomarkers (Trollor et al., 2010) and WM integrity (Fields, 2008) have been closely linked to cognitive performance, and the established influences of peripheral inflammation on brain WM (Shoamanesh et al., 2015; Wersching et al., 2010), it is logical to expect that WM integrity may act as a mediator in the associations between peripheral inflammation and cognition. Two recent studies have confirmed the mediation effects of GM volumes in the relationships of peripheral inflammation with cognitive performance (Jiang et al., 2015; Marsland et al., 2015). Whether WM integrity also mediates these relationships remains uncertain.

While studies using animal models suggested that MIC-1/GDF15 may be anti-inflammatory, neurotrophic and neuroprotective, serum MIC-1/GDF15 levels were found to increase in inflammatory conditions such as rheumatoid arthritis (Brown et al., 2007) and atherosclerosis (Brown et al., 2002b), and negatively associated with cognitive performances (Fuchs et al., 2013). Therefore, we hypothesized that elevated MIC-1/GDF15 serum levels would also be associated with WM degeneration, and this association was more obvious in MCI than CN. Furthermore, WM integrity is one of the underlying mechanisms for the previously observed negative relationship between MIC-1/GDF15 serum levels and cognition.

2. Material and methods

2.1. Participants

The participants were drawn from Sydney Memory and Ageing Study (MAS), of which the methodological details and inclusion criteria have been described previously (Sachdev et al., 2010; Tsang et al., 2013). Briefly, following a random approach, 1037 non-demented community-dwelling participants aged 70–90 were initially recruited from 8914 individuals registered in the electoral roll of two regions in Sydney, Australia from September 2005 to November 2007 (Wave 1). Individuals were excluded if they had insufficient English to complete the assessments, a diagnosis of dementia or a Mini-Mental State Examination (MMSE) score (Folstein et al., 1975) of less than 24 adjusted for age, years of education and non-English speaking background (NESB), psychotic symptoms, schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy or other conditions that may affect the completion of assessments. Two years later, 889 participants were followed up (Wave 2). The inclusion of participants in the current study was based on the availability of both blood tests and MRI scans. Even though two waves of MAS data are currently available, we only included Wave 2 data in the current study, because we had better image quality for the diffusion tensor imaging (DTI) data at Wave 2 (32 directions) compared to Wave 1 (6 directions). At Wave 2, 585 individuals received blood tests for MIC-1/GDF15 serum levels, and 420 underwent MRI scans. 327 participants with both MIC-1/GDF15 serum levels and MRI acquired were included in the current study (Table 1). All participants gave written informed consent. Ethics approval was obtained from the Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service.

Diagnosis of MCI was made by using the recent international consensus criteria (Winblad et al., 2004). Criteria include (1) complaint of decline in memory or other cognitive functions from the participants or a knowledgeable informant; (2) generally intact instrumental activities of daily living (IADL), measured by an average score of less than 3.0 on the Bayer ADL Scale adjusted for physical impairment (Hindmarch et al., 1998); (3) objective cognitive impairment defined as at least 1.5 standard deviation (SD) below the normative data on any one neuropsychological test; and (4) mini-mental state examination (MMSE) score of $\geq$24 adjusted for age and years of education.

2.2. Serum MIC-1/GDF15 levels measurement

All blood sampling was done in the morning after an overnight fast. The serum was stored at −80 °C for later analyses. The MIC-1/GDF15 serum level concentration was determined by an enzyme-linked immunosorbent assay (ELISA). The procedures were previously described in detail (Brown et al., 2002a).

2.3. Magnetic resonance imaging (MRI)

MRI scans of all participants were acquired on a Philips 3T Achieva Quasar Dual scanner. The acquisition parameters for each protocol are: