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Serum IL-7 and G-CSF in major depressive disorder

Soili M. Lehto [a,*], Anne Huotari [b,c], Leo Niskanen [d], Karl-Heinz Herzig [a,b,c], Tommi Tolmunen [a], Heimo Viinamäki [a], Heli Koivumaa-Honkanen [a,e,f], Kirsi Honkalampi [g], Sanna Sinikallio [h], Heli Ruotsalainen [c], Jukka Hintikka [a]

[a] Department of Psychiatry, Kuopio University Hospital and University of Eastern Finland, 70210 Kuopio, Finland
[b] Department of Pharmaceutics, University of Kuopio, Finland
[c] Institute of Biomedicine, Division of Physiology and Biocenter Oulu, University of Oulu, Finland
[d] Department of Medicine, Kuopio University Hospital and University of Eastern Finland, 70210 Kuopio, Finland
[e] Department of Clinical Medicine, University of Oulu, Finland
[f] Department of Psychiatry, Lapland Hospital District, 97140 Rovaniemi, Finland
[g] Kuopio Psychiatric Center, P.O. Box 1777, 70211 Kuopio, Finland
[h] Department of Rehabilitation, Kuopio University Hospital, Kuopio, Finland

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ABSTRACT

Major depressive disorder (MDD) has been associated with dysregulated immune systems and impaired T cell function, but data on depression-related alterations in the levels of immunomodulatory growth factors are scarce. In order to further clarify the mechanisms underlying immune system dysregulation in depressed subjects, we examined the associations between MDD and serum levels of two immunomodulatory growth factors, interleukin (IL)-7 and granulocyte-colony stimulating factor (G-CSF), in 122 subjects (MDD with long-term symptomatology, $n=61$; controls, $n=61$). The MDD subjects had lowered levels of IL-7. In a model adjusted for age, gender and body mass index, subjects in the lowest tertile of IL-7 had a 3.4-fold increased likelihood for MDD ($p=0.010$). Further adjustments for sleep disturbances, alcohol use, smoking, and metabolic syndrome did not alter these findings. Moreover, the exclusion of subjects with rheumatoid arthritis, coronary heart disease, or the use of non-steroidal anti-inflammatory medications or oral corticosteroids only slightly attenuated the findings. The G-CSF levels did not differ between the two groups. The lowering of the serum levels of IL-7, a regulator of T cell homeostasis, in MDD subjects may underlie the depression-related impaired T cell function.

1. Introduction

Enhanced low-grade inflammation has been linked to major depressive disorder (MDD) (Raison et al., 2006; Schiepers et al., 2005). However, a simultaneous impairment of T cell functions has also been reported (Irwin and Miller, 2007). Smith (1991) proposed in his macrophage theory of depression that depression is characterized by increased secretion of macrophage cytokines such as IL-1 and TNF, and suppression of the secretion of T cell-derived lymphokines. In concordance with this theory, IL-6, also a macrophage product, has been demonstrated to be elevated in depression in a recent meta-analysis (Dowlati et al., 2010). The association between depression and elevated inflammatory status is likely to be bidirectional; enhanced inflammation predisposes to depression (Gimeno et al., 2009), and depression leads to systemic inflammation (Stewart et al., 2009).

A growth factor and cytokine, IL-7 is considered to be an immunostimulatory substance and a major homoeostatic cytokine (Calzascia et al., 2008). It is essential for lymphocyte development and survival (Jiang et al., 2005), and also induces the production of inflammatory cytokines from T cells (Kim et al., 2008). It additionally regulates T cell homoeostasis through (a) modulating thymic output, (b) stimulating the expansion and survival of naïve and memory T cells, and (c) inhibiting T cell apoptosis (Kim et al., 2008). Therefore, through the regulation of T cells, which secrete lymphokines, IL-7 also participates in the cascade possibly contributing to the hypothesized depression-related lymphokine suppression (Smith, 1991). However, data on the levels of IL-7 in depressed subjects are scarce. One previous

Abbreviations: ADS, atypical depression supplement; BDI, Beck Depression Inventory; BMI, body mass index; CNS, central nervous system; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbant assay; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; HAM-D, Hamilton depression rating scale; HDL-C, high-density lipoprotein cholesterol; HMS, high mental symptom group; IL, interleukin; KUDEP, Kuopio Depression Study; LDL-C, low-density lipoprotein cholesterol; LMS, low mental symptom group; LS, Life Satisfaction; MDD, major depressive disorder; MetS, metabolic syndrome; NSAID, non-steroidal anti-inflammatory drug; SCID, Structured Clinical Interview for DSM-IV; TAS, Toronto Alexithymia Scale; TC, total cholesterol; TG, triglycerides; Th cells, T helper cells..

* Corresponding author. Tel.: +358 40 8277 973; fax: +358 17 17 2966.
E-mail address: Soili.Lehto@kuh.fi (S.M. Lehto).

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study has reported elevated serum levels of IL-7 in MDD (Simon et al., 2008).

In addition to mediating inflammation, some growth factors also have various other functions in the central nervous system (CNS). Granulocyte-colony stimulating factor (G-CSF), a member of the hematopoietic growth factor family, is considered to have both anti-inflammatory and neuro-protective properties (Kleinschnitz et al., 2004; Schneider et al., 2005a). Recent data have also demonstrated that G-CSF receptors are expressed by the CNS neurons and glial cells (Schneider et al., 2005b). Furthermore, G-CSF is considered to be a candidate for the treatment of neurodegenerative conditions (Schneider et al., 2005a). To the best of our knowledge, however, no previous studies have evaluated the role of circulating G-CSF in depression. Nevertheless, depression-related neurodegenerative processes have been suggested to be at least partially induced by disturbances of inflammatory systems (Maes et al., 2009). Thus, alterations should be observable in neuro-protective, anti-inflammatory growth factors such as G-CSF.

In contrast to previous reports of elevated levels of inflammatory markers in depression, some recent studies have suggested the opposite. Lowered levels of cytokines or genetic alterations leading to lowered production of C-reactive protein (CRP) have been independently associated with depression (Almeida et al., 2009; Lehto et al., 2010a; Whooley et al., 2007). In addition to the discrepancy observed with regard to inflammatory alterations in MDD, the mechanisms underlying depression-related T cell pathology are unclear and in need of further clarification (Miller, 2010). Since IL-7 is a major regulator of T cell functioning, its measurement could potentially elucidate the observed depression-related T cell alterations.

In order to further investigate MDD-related alterations of inflammatory systems, we examined the serum levels of immunomodulatory growth factors IL-7 and G-CSF in 122 subjects in a population-based sample.

2. Methods

2.1. Study setting and subjects

This study formed a clinical arm of the Kuopio Depression (KUDEP) four-phase general population study focusing on the mental health of general population adults aged 25–64 years. It was conducted in the province of Kuopio in Eastern Finland. A random sample of 3004 participants was selected in 1998 via the National Population Register. The same sample was followed up in 1999 and 2001. The baseline sample (in 1998) comprised 2050 participants, the first follow-up sample in 1999 a total of 1722 participants, and the second follow-up sample in 2001 a total of 1593 participants. The follow-up questionnaire in 2001 was only sent to those participants who responded at baseline or in 1999. For the non-respondents at each follow-up, the questionnaire was mailed again one month later. In the questionnaire, participants reported their age, gender, marital status (married or living with a partner vs. unmarried, separated or divorced, widowed, other), alcohol use (≥2 times per week vs. less), number of cigarettes smoked daily, the presence of sleep disturbance (no disturbances or mild disturbances vs. moderate, severe or very severe difficulty in sleeping), the use of psychiatric medications during the past week (antidepressants, antipsychotics, anxiolytics; yes/no), and previous physician-diagnosed somatic illnesses (yes/no).

In the fourth study phase in 2005, a sub-sample of the previous study phases ($n=427$) was offered a possibility to participate in a clinical evaluation and laboratory testing (Lehto et al., 2010; Viinamäki et al., 2009). The inclusion criteria for this study sample were based on the presence or absence of self-reported adverse mental symptoms prevailing at baseline and in both follow-ups. Half of the selected subjects reported elevated Beck Depression Inventory scores (BDI-21 score>9) (Beck et al., 1961), alexithymic features according to the Toronto Alexithymia Scale (TAS-20 score>58) (Bagby et al., 1994a, 1994b) or life dissatisfaction with the Life Satisfaction scale (LS score>11) (Koivumaa-Honkanen et al., 2000) in the three assessments. In all study phases, the subjects who displayed elevated BDI scores were further directed to mental health care services. In addition to those who fulfilled the previous criteria (i.e. high mental symptom group, HMS; $n=209$), a group of those not fulfilling them (i.e. low mental symptom group, LMS; $n=218$) was formed with the same age and gender distribution as among those with chronic adverse symptoms. The final participation rate was 78% ($n=333$).

A trained, experienced research nurse conducted the psychiatric interviews for all study participants, including the controls, by using the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II; American Psychiatric Association, 1994). A total of 61 participants were diagnosed with current MDD. All MDD subjects had MDD as a primary diagnosis, and those with bipolar disorders were excluded. A healthy control group ($n=61$) with an age and gender distribution similar to that of the MDD group was formed among LMS participants who consistently reported low BDI scores in 1998, 1999 and 2001. The mean BDI scores (SD) for the MDD group were 18.7 (9.4) in 1998, 21.6 (9.8) in 1999 and 21.1 (11.2) in 2001. In the control group the respective mean scores (SD) were 2.6 (2.2) in 1998, 2.9 (2.6) in 1999 and 2.1 (1.9) in 2001. Data on the use of somatic medications of the participants during the study period were acquired from the register of the National Agency for Medicines and the Social Insurance Institute.

The assessment of depression severity was conducted with the 29-item Hamilton Depression Rating Scale (HAM-D-29; Williams and Terman, 2003) by the same interviewer during the same appointment as the SCID interviews. The HAM-D-29 consists of the 21-item Hamilton Depression Rating Scale (HAM-D-21) with a supplementary 8-item subscale (Atypical Depression Supplement, ADS) for scoring atypical features of depression. The ADS includes questions concerning weight gain, increased appetite/eating, carbohydrate craving, hypersomnia, leaden paralysis and social withdrawal.

Approval for the study was obtained from the Ethics Committee of Kuopio University Hospital and the University of Kuopio, and the study protocol was in accordance with the latest version of the Declaration of Helsinki. All participants provided written informed consent before entering the study.

2.2. Measurements

The laboratory measurements were carried out in the accredited Kuopio University Hospital medical laboratory. The subjects came for venous blood sampling at 8 am, after having been instructed to fast for the previous 12 h. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and fasting plasma glucose measurements were carried out according to the routine protocols. Enzymatic methods (Thermo Electron Co, Finland) were used for all measurements (TC: Konelab CHOLESTEROL, code 981812; HDL-C: Konelab HDL-CHOLESTEROL, code 981655; TG: Konelab TRIGLYCERIDES, code 981301; fasting plasma glucose: Konelab GLUCOSE, code 981304). The total variations in the utilized methods were 1.6%, 3.7%, 4.8% and 3.1%, respectively. The samples were analyzed using a Konelab 60i Clinical Chemistry Analyzer (Thermo Electron Co).

For the analyses of growth factors, the venous blood samples were stored at −80 °C until run. The levels of IL-7 (pg/mL) and G-CSF (pg/mL) were analyzed by multiplexing with Bio-Plex Human Cytokine Panel 1 utilizing a Bio-Plex instrument based on Luminex xMAP technology (Bio-Rad Laboratories Inc., CA, US), which provides an average value based on 100 bead measurements. The Luminex method and enzyme-linked immunosorbant assay (ELISA), the gold standard of current peptide immunoassays, are highly correlated (de Jager, 2003; Elshal and McCoy, 2006; Leng et al., 2008). Before analyses, the samples were centrifuged for 15 min at 3000 rpm, and diluted 1:2 in an appropriate sample matrix. The assay conditions were standardized and pre-optimized to ensure optimal reproducibility of the assays, and the kit