Brain, Behavior, and Immunity 40 (2014) 235–243

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Expression of Toll-Like Receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder

Szabolcs Kéri [a,b,c,*], Csilla Szabó [b], Oguz Kelemen [d]

[a] Department of Cognitive Science, Budapest University of Technology and Economics, Budapest, Hungary
[b] Nyírő Gyula Hospital – National Institute of Psychiatry and Addictions, Budapest, Hungary
[c] Department of Physiology, Faculty of Medicine, University of Szeged, Szeged, Hungary
[d] Bács-Kiskun County Hospital, Psychiatry Center, Kecskemét, Hungary

ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form 25 March 2014
Accepted 28 March 2014
Available online 12 April 2014

Keywords:
Major depressive disorder
Inflammation
Toll-Like Receptors
Cognitive-behavioral therapy

ABSTRACT

In recent years, increased attention has been paid to the inflammatory mechanisms of major depressive disorder (MDD). The aim of the present study was to investigate pro-inflammatory pathways related to the "leaky gut" hypothesis of MDD, which is based on the putative intestinal translocation of Gram-negative bacteria and a subsequent abnormal immune response mediated by the Toll-Like Receptor-4 (TLR-4) pathway. 50 patients with first-episode MDD and 30 healthy control subjects participated in the study. Real-time quantitative PCR was used to measure TLR-4 and TLR-2 RNA from peripheral mononuclear blood cells, as well as the expression of NF-κβ, a key transcription factor of the pro-inflammatory response. TLR-4 protein expression was determined by using flow cytometry. TLR-2 served as a control molecule. Low-grade inflammation was characterized by the measurement of interleukin-6 (IL-6) and C-reactive protein (CRP). Bacterial translocation was investigated by the measurement of the 16S rRNA subunit (16S rDNA) of intestinal microbiota in the blood plasma of the participants. We performed these analyses before (t1) and after (t2) cognitive-behavioral therapy (CBT) in MDD. The healthy control subjects were also assessed two times. We found significantly elevated expressions of all three markers (TLR-4 RNA and protein, NF-κβ RNA) and 16S rDNA in MDD at t1 relative to healthy control subjects. These markers showed a significant decrease during CBT (t1 > t2 in MDD). We observed no between-group differences and changes in the case of TLR-2. Greater reduction of pro-inflammatory markers during CBT was associated with more pronounced clinical improvement. IL-6 and CRP displayed a moderately elevated level in MDD and did not change during CBT. In conclusion, TLR-4 signaling is up-regulated in newly diagnosed patients with MDD, which may be related to bacterial translocation or to the presence of various damage-associated molecular patterns. Clinical improvement during psychotherapy is associated with decreased expression of pro-inflammatory markers.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Since the pioneering work revealing decreased lymphocyte proliferation in response to mitogens (Kronfol et al., 1983; Schleifer et al., 1984), a multitude of studies have indicated altered immune responses and increased low-grade inflammation in major depressive disorder (MDD) (Dowlati et al., 2010; Frodl and Amico, 2014; Herbert and Cohen, 1993; Licinio and Wong, 1999; Maes, 2011; Miller et al., 2009a,b; Raedler, 2011). Inflammatory mechanisms mediated by various cytokines and other mediator substances interact with the hypothalamic–pituitary–adrenal gland (HPA) stress axis, neurotransmitter metabolism and may have a profound influence on neuronal plasticity linked to depressive symptoms. Despite the fact that research studies explored various facets of inflammatory mechanisms, it is still not clear why we can see enhanced pro-inflammatory activity in MDD. In a recent review and synthesis of the literature, Berk et al. (2013) identified several factors that elevate the risk of MDD and other common somatic

* Corresponding author at: Department of Physiology, Faculty of Medicine, University of Szeged, Dóm sq. 10, H6720, Szeged, Hungary. Tel.: +36 20 448 3530; fax: +36 62 545 842.
E-mail addresses: keri.szabolcs.gyula@med.u-szeged.hu, szkeri2000@yahoo.com (S. Kéri).

http://dx.doi.org/10.1016/j.bbi.2014.03.020
0889-1591/© 2014 Elsevier Inc. All rights reserved.

diseases probably by causing low-grade inflammation; these risk factors include psychosocial stressors, "Western-type" diet containing nutrients with high refined carbohydrates and saturated fatty acids, low physical activity, smoking, obesity, and vitamin D deficiency.

A new mechanism that may play a role in MDD-associated inflammation is increased gut permeability, bacterial translocation, and a subsequent activation of the Toll-Like Receptor (TLR) pathway (Berk et al., 2013; Lucas and Maes, 2013; McCusker and Kelley, 2013). TLRs are pattern recognition receptors in sentinel cells (e.g., macrophages) that are responsible for the detection of characteristic molecules of pathogens and to initiate the first line of the innate immune response (Leulier and Lemaitre, 2008). Research revealed an increase in immunoglobulin production against the lipopolysaccharide (LPS) component of certain Gram-negative bacteria in MDD (Maes et al., 2008, 2012, 2013). These microorganisms are part of the normal gut flora in healthy individuals. However, bacterial translocation may lead to abnormal immune activation in MDD. Under normal circumstances, Gram-negative bacteria are separated from the lymphatic system and systematic circulation by tight junctions between the epithelial cells of the gut. If this barrier is weakened ("leaky gut"), Gram-negative bacteria will have a contact with the immune system eliciting an abnormal response in MDD (Maes et al., 2008, 2012, 2013).

Gárate et al. (2011, 2013) developed a new animal model of depression that tested the "leaky gut" mechanism. The authors showed that chronic mild stress increased bacterial LPS in the circulation of rats and a subsequent activation of the TLR-4 pathway that may be, at least in part, responsible for behavioral despair in animals (Gárate et al., 2011). TLR-4 and its co-receptor, myeloid differentiation protein-2 (MD-2), recognize bacterial LPS and in turn activate a network of intracellular cascade in which the transcription factor Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells (NF-κβ) is a central hub. NF-κβ activates the expression of pro-inflammatory cytokines, such an interleukin-1 (IL-1) and Tumor Necrosis Factor-β (TNF-β), and facilitates the synthesis of arachidonic-acid derivates (Feng et al., 1995; Verstrepen et al., 2008). Exposition to stress upregulates the TLR-4 pathway in the frontal cortex of mice, leading to the activation of NF-κβ and pro-inflammatory enzymes (nitric oxide synthase and cyclooxygenase-2), which will ultimately result in oxidative and nitrosative cellular damage (Gárate et al., 2013). Evidence also indicates that intestinal decontamination with antibiotics prevents stress-induced elevation of LPS binding protein in the circulation and TLR-4 activation in the frontal cortex of experimental animals (Gárate et al., 2013).

The purpose of the present study was to examine the translational potential of these findings in human patients. We investigated TLR-4-related mechanisms in newly diagnosed, drug-free patients experiencing their first lifetime major depressive episode. In addition, we repeated these assessments after a complete series of sessions of cognitive-behavioral therapy (CBT) to better understand how behavioral and cognitive interventions may affect inflammatory mechanisms in MDD. We studied the expression of TLR-4 at the mRNA and receptor protein level, together with the expression of NF-κβ. TLR-2 served as a control molecule because it is not activated by Gram-negative bacteria (Akira et al., 2006; Leulier and Lemaitre, 2008; Liu et al., 2013). In addition, low-grade, non-specific systemic inflammation was characterized by the measurement of IL-6 and C-reactive protein (CRP), two markers proven by meta-analyses in MDD (Hiles et al., 2012; Howren et al., 2009; Kuo et al., 2005). Finally, we intended to test the "leaky gut" hypothesis of MDD by investigating markers related to gut barrier permeability and bacterial translocation. Specifically, we measured the plasma levels of the well-conserved 16S ribosomal RNA (rRNA) subunit (16S rDNA) of intestinal microbiota, which is an accepted indicator of bacterial translocation with a better reliability than LPS assays (Jiang et al., 2009; Kane et al., 1998; Swidsinski et al., 2007).

We had the following hypotheses: (1) In line with an increased level of the 16S rRNA subunit of intestinal microbiota, we expected that TLR-4, but not TLR-2, would be up-regulated in untreated patients with MDD. This hypothesis was based on the assumption that bacterial translocation would lead to the activation of TLR-4. (2) We also hypothesized that the activation of TLR-4 would result in an increased level of low-grade inflammation, as revealed by previous meta-analyses (Hiles et al., 2012; Howren et al., 2009; Kuo et al., 2005). (3) Finally, we expected that effective psychological intervention (CBT) would lead not only to the reduction of clinical symptoms, but also to the normalization of the TLR-4 pathway and low-grade inflammation.

2. Methods

2.1. Participants

The patients were enrolled at the National Institute of Psychiatry and Addictions, Budapest, and in two South-Hungarian counties (Csongrád and Bács-Kiskun). Practitioners referred first-episode patients with MDD without a history of previous treatment. We also enrolled healthy control participants with negative history for mental disorders via internet and local advertisements. The trained and supervised clinical raters who assessed the participants were blind to the aim of the study and did not have any information about the initial diagnosis before the assessment. All participants received the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al., 1996) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). All patients received the diagnosis of major depressive episode (mean duration of untreated episode: 4.3 months, SD = 6.3). There were no Axis I disorders in the control group. The Hollingshead Four Factor Index (Hollingshead, 1975) was used to characterize the socioeconomic status of the participants. This index takes into consideration education, occupation, gender, and marital status (score range: 8–66). We matched patients and controls for socioeconomic status because evidence suggests its significant relationship with inflammation (Chen and Miller, 2013). The patients did not receive any pharmacological treatment or psychotherapy before the study. We did not administer psychotropic drugs during CBT. Exclusion criteria included presence and history of psychotic or manic symptoms, severe suicidality requiring emergency treatment and crisis intervention, substance misuse in the past 6 months, general health problems requiring medications, and inability or unwillingness to participate in the psychotherapeutic process. The demographic data are summarized in Table 1. The study was done in accordance with the Declaration of Helsinki and was approved by the national and institutional ethics boards. All participants provided written informed consent.

2.2. Blood sample

50 patients provided blood samples before CBT (t1) and 43 patients provided blood samples after CBT (t2) (between 8:00 and 9:00 a.m. before breakfast). To ensure the test–retest reliability of the measurements, we also obtained blood samples from the control subjects at t1 and t2. One control subject did not provide blood sample at t2. The analysis was performed by skilled biotechnicians who were not aware of the diagnosis and assessment session (t1 or t2). All analyses were repeated by the authors. We compared 50 patients with MDD and 30 control subjects at t1 with 43 patients and 29 controls at t2. We also performed control analyses excluding the participants who did not provide blood samples

Download English Version:

https://daneshyari.com/en/article/921984

Download Persian Version:

https://daneshyari.com/article/921984

Daneshyari.com