Increased serum levels and promoter polymorphisms of macrophage migration inhibitory factor in schizophrenia

Satoshi Okazaki\textsuperscript{a}, Akitoyo Hishimoto\textsuperscript{a,⁎}, Ikuo Otsuka\textsuperscript{a}, Yuichiro Watanabe\textsuperscript{b}, Shusuke Numata\textsuperscript{c}, Shuken Boku\textsuperscript{a}, Naofumi Shimmyo\textsuperscript{a}, Makoto Kinoshita\textsuperscript{c}, Emiko Inoue\textsuperscript{b}, Tetsuro Ohmori\textsuperscript{c}, Toshiyuki Someya\textsuperscript{b}, Ichiro Sora\textsuperscript{a}

\textsuperscript{a} Department of Psychiatry, Kobe University Graduate School of Medicine, Kobe, Japan
\textsuperscript{b} Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
\textsuperscript{c} Department of Psychiatry, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan

ARTICLE INFO

Keywords:
Schizophrenia
MIF
Serum protein
Postmortem brain
Microsatellite

ABSTRACT

Background: Numerous studies have suggested that an immune system imbalance plays an important role in schizophrenia. Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine. It plays multiple roles in various biological processes, including inflammation and neurogenesis. Furthermore, several exhaustive serum proteomic profiling studies have identified MIF as a potential biomarker of schizophrenia. Here, we investigate MIF protein levels in serum and postmortem prefrontal cortex in patients with schizophrenia and controls. Moreover, we investigate the association of two functional polymorphisms in the MIF gene promoter region (MIF-794CATT\textsubscript{8}\textsuperscript{a} microsatellite and MIF-173G/C single-nucleotide polymorphism [SNP]) with schizophrenia.

Methods: We measured serum MIF levels with an enzyme-linked immunosorbent assay (ELISA) (51 patients vs. 86 controls) and postmortem brain MIF levels with a western blotting assay (18 patients vs. 22 controls). Subsequently, we genotyped the MIF-794CATT\textsubscript{8}\textsuperscript{a} microsatellite with a fluorescence-based fragment assay and the MIF-173G/C SNP with a TaqMan SNP genotyping assay (1483 patients vs. 1454 controls).

Results: Serum MIF levels were significantly higher in patients with schizophrenia than in controls (p = 0.00118), and were positively correlated with antipsychotic dose (Spearman’s r = 0.222, p = 0.0402). In addition, an earlier age of onset was observed in patients with a high serum MIF level (> 40 ng/mL) than those with a low serum MIF level (< 40 ng/mL) (p = 0.0392). However, postmortem brain MIF levels did not differ between patients with schizophrenia and controls. The association study revealed that the CATT\textsubscript{8}G haplotype was significantly associated with schizophrenia (p = 0.0338), and that the CATT\textsubscript{8} allele and CATT\textsubscript{8}G haplotype were significantly associated with female adolescent-onset schizophrenia (AoS) (corrected p = 0.0222 and p = 0.0147, respectively).

Conclusions: These results suggest that serum MIF level is a potential pharmacodynamic and/or monitoring marker of schizophrenia, and is related to a novel antipsychotic effect beyond dopamine antagonism. Furthermore, the MIF gene polymorphisms are associated with the risk for schizophrenia especially in adolescent females, and are potential stratification markers of schizophrenia. Further studies of MIF are warranted to elucidate the pathophysiology of schizophrenia and the effects of antipsychotics.

1. Introduction

Schizophrenia is a chronic and disabling psychiatric illness affecting around 1% of the general population (Mueser and McGurk, 2004). Numerous genetic studies, including twin research, have suggested that a large number of genetic and environmental factors contribute to the development of schizophrenia (Harrison and Owen, 2003; Sullivan et al., 2003). Recent genome-wide association studies (GWASs) suggest that many polymorphisms contribute to the risk of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

Abbreviation: AoOS, adolescent-onset schizophrenia; AoOS, adult-onset schizophrenia; BPRS, Brief Psychiatric Rating Scale; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; ELISA, enzyme-linked immunosorbent assay; GAF, Global Assessment of Functioning; GWAS, genome-wide association study; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; MIF, macrophage migration inhibitory factor; PCR, polymerase chain reaction; PMI, postmortem interval; SNP, single nucleotide polymorphism

⁎ Corresponding author: Department of Psychiatry, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
E-mail address: hishipon@med.kobe-u.ac.jp (A. Hishimoto).

https://doi.org/10.1016/j.pnpbp.2018.01.001
Received 13 September 2017; Received in revised form 1 January 2018; Accepted 1 January 2018
Available online 02 January 2018
0278-5846/© 2018 Elsevier Inc. All rights reserved.
However, it remains unclear which genetic and environmental abnormalities are essential in the pathophysiology of schizophrenia.

In recent decades, cytokine imbalances have been consistently reported in patients with schizophrenia (Avgustin et al., 2005; Katila et al., 1994; Monji et al., 2009; Muller et al., 1999; Potvin et al., 2008; Schmitt et al., 2005; Schwarz et al., 2001; Watanabe et al., 2010). Cytokines are active in infection and inflammation, and mediate cross-talk between the brain and immune system (Rothwell, 1999). They are released from various blood cells such as macrophages, monocytes, T cells, and B cells. In the brain, they areexpressed by neurons, astrocytes, and microglia, and mayregulate brain development (Mehler and Kessler, 1997; Vitkovic et al., 2000).

Macrophage migration inhibitory factor (MIF) is a pleotropic cytokine involved in the regulation of innate and adaptive immunity (Calandra and Roger, 2003). MIF was one of the first cytokines to be discovered and was originally identified as a T cell-derived factor that inhibited the random migration of macrophages (Bloom and Bennett, 1966; David, 1966). MIF is secreted in response to inflammatory stimuli, including microbial products and glucocorticoids (Bernhagen et al., 1993; Calandra et al., 1995). Upon release, MIF counter-regulates the immunosuppressive activity of glucocorticoids and promotes the expression and secretion of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, IL-8, tumor necrosis factor-α, and interferon-γ (Calandra et al., 1995; Calandra and Roger, 2003; Flaster et al., 2007). MIF is also a functional noncognate ligand for the chemokine receptors CXCR2/4, controlling inflammatory and atherogenic cell recruitment (Bernhagen et al., 2007). Moreover, MIF has also been shown to facilitate the DNA damage response and cell cycle regulation (Flaster et al., 2007), enhance autophagy (Chuang et al., 2012), and is associated with the hypothalamic–pituitary–adrenal axis (Bernhagen et al., 1994; Calandra et al., 1995). In addition to its presence in the immune system, MIF has a broad tissue distribution including the anterior pituitary, liver, kidneys, adrenal glands, pancreas, testes, and brain (Calandra and Roger, 2003; Kleemann et al., 2000).

MIF expression in the brain was identified in neurons of the cortex, hypothalamus, hippocampus, cerebellum, and pons (Bacher et al., 1998), as well as in astrocytes and the sub-granular zone of the hippocampus (Conboy et al., 2011). Previous studies suggest that MIF plays an important role in neurogenesis and neural protection by supporting the proliferation and survival of neural stem cells via multiple signaling pathways (Ohba et al., 2012, 2013, 2016). However, MIF is implicated in various biological processes including inflammation, as outlined above. Therefore, the role of MIF in neurological disorders appears to be diverse, with both beneficial and adverse effects (Leyton-Jaimes et al., 2017). MIF plays an important role in enhancing tumorigenic processes (Amin et al., 2003; Chesney et al., 1999; Lacey et al., 2003) and Alzheimer's disease (Bacher et al., 2010; Oyama et al., 2000; Popp et al., 2009). Moreover, MIF levels increase with the severity of autism-spectrum disorders (Grigorenco et al., 2008) and spinal cord injury (Bank et al., 2015; Koda et al., 2004; Stein et al., 2013). In contrast, the protective effect of MIF against amyotrophic lateral sclerosis has been reported (Israelson et al., 2015; Leyton-Jaimes et al., 2016). Intriguingly, both protective and pathological roles of MIF have been implicated in stroke and cerebral ischemia (Amaral et al., 2007; Koga et al., 2011; Miller et al., 2008; Wang et al., 2009), as well as depression (Bay-Richter et al., 2015; Bloom and Al-Abed, 2014; Cattaneo et al., 2013; Conboy et al., 2011; Fan et al., 2014; Gellen et al., 2017; Moon et al., 2012; Musli et al., 2011).

Recently, several exhaustive serum proteomic profiling studies have identified MIF as a potential biomarker for schizophrenia (Chan et al., 2015; Schwarz et al., 2012; Schwarz et al., 2010, 2014). In addition, the MIF gene is located on chromosome 22q11.2, in which deletions are well known to increase the risk for psychiatric/behavior problems such as schizophrenia (Bassett et al., 2008; Hiroi et al., 2013). In 22q11.2 deletion syndrome, there is deletion or duplication of various intervals in this region, which are classified as proximal, central, and distal deletions (Burnside, 2015). Proximal deletions, including DiGeorge syndrome interval, are common recurrent microdeletions, and increase the risk for psychiatric/behavior problems (~60%). Rare distal deletions, including the MIF gene, also increase the risk for psychiatric/behavior problems (25%) (Burnside, 2015). Furthermore, a signaling pathway via the chemokine receptor CXCR4, which is one of the receptors of MIF, was reported to be involved in DiGeorge/22q11-deletion syndrome (Duhand et al., 2016; Toritsuka et al., 2013).

These findings lead to the hypothesis that MIF is involved in the pathophysiology of schizophrenia. To elucidate the association of MIF with schizophrenia, we examined serum MIF levels derived from patients with schizophrenia and controls. Subsequently, we examined MIF protein levels in the prefrontal cortex of postmortem brain samples from patients with schizophrenia and controls. Finally, we conducted an association study of two functional polymorphisms in the MIF gene promoter region with schizophrenia.

2. Methods

2.1. Participants

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of each participating institute. After a complete description of the study, written informed consent was obtained from all participants for the serum and genetic studies, and from close relatives of participants for the postmortem brain study. All participants were of Japanese descent.

In the serum MIF levels study, the cohort consisted of 86 patients with schizophrenia (46 men and 40 women; mean age ± SD, 54.3 ± 10.3 years) and 51 controls (23 men and 28 women; 48.4 ± 9.5 years), who were recruited from Kobe University (47 patients and 11 controls) and Tokushima University (39 patients and 40 controls). Demographic and clinical characteristics are shown in Supplementary Table 1a. The antipsychotic dose of each patient was estimated at the time of blood collection. In the postmortem brain MIF levels study, the cohort consisted of 18 patients with schizophrenia (9 men and 9 women; 60.1 ± 17.0 years) and 22 controls (17 men and 5 women; 56.0 ± 17.3 years), who were recruited from Kobe University. The demographic data, postmortem interval (PMI), and pH of the preservative solution of postmortem brain samples are shown in Supplementary Table 1b. In the MIF gene polymorphisms association study, the cohort consisted of 1483 patients with schizophrenia (796 men and 687 women; 46.4 ± 15.6 years) and 1454 controls (709 men and 745 women; 46.6 ± 17.0 years), who were recruited from Kobe University (721 patients and 743 controls), Tokushima University (31 patients and 39 controls), and Niigata University (731 patients and 672 controls), and included some participants from the serum study. Accurate information about age of onset was available from the clinical records of 1263 (85%) of our 1483 patients. We subdivided the patients with schizophrenia into two groups according to age at first onset: adolescent-onset schizophrenia (AsOS, age of onset < 21 years) and adult-onset schizophrenia (AtOS, age of onset ≥ 21 years) in reference to Basso et al. (Basso et al., 1997). There were 486 patients with AsOS (260 men and 226 women; 37.9 ± 14.5 years), and 777 patients with AtOS (413 men and 364 women; 49.4 ± 14.1 years). Demographic and clinical characteristics are shown in Supplementary Table 1c.

Psychiatric assessments of participants were performed as previously described (Okazaki et al., 2016; Otsuka et al., 2015). In the serum MIF levels and the MIF gene association studies, a diagnosis of schizophrenia was given by at least two psychiatrists according to the DSM-IV or DSM-5 criteria for schizophrenia based on unstructured interviews and reviews of their medical records. Control participants were healthy volunteers, screened for psychiatric disorders by a psychiatrist. None had any present, past, or family (first-degree relatives) history of psychiatric disorders or substance abuse, excluding nicotine dependence. In the postmortem brain study, a diagnosis of...
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهرهمندی از سیستم هوشمند رهگیری سفارشات