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Altered chemokine levels in the cerebrospinal fluid and plasma of suicide attempters

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TARC

Summary Chemokines constitute a class of small inflammatory proteins that control the chemotaxis of leukocytes. They are also present in the central nervous system (CNS) and contribute to diverse physiological functions, such as the regulation of cell migration, axonal growth and neuronal survival. It is to date not known whether chemokines in the CNS are affected in psychiatric disorders. In this study, chemokine levels were measured in the cerebrospinal fluid (CSF) of 137 psychiatric patients in conjunction to a suicide attempt, and 43 healthy controls. A subgroup of patients ($n = 42$) was followed up with blood samples 12 years after the initial CSF collection, when they did not show suicidal behavior. The follow-up chemokine levels were compared to those of psychiatric patients ($n = 17$) who had never attempted suicide. Ultra-sensitive chemokine multiplex immunoassay was used to quantify eotaxin-1 (CCL11), interferon gamma-induced protein-10 (IP-10, CXCL10), macrophage inflammatory protein-1β (MIP-1β, CCL4), monocyte chemotactic protein-1 (MCP-1, CCL2), MCP-4 (CCL13) and thymus and activation regulated chemokine (TARC, CCL17). Patients were diagnosed using DSM-III-R/DSM-IV, and assessed using the Comprehensive Psychopathological Rating Scale (CPRS), including subscales, and the Suicidal Intent Scale (SIS). CSF eotaxin-1, MIP-1β, MCP-1, MCP-4 and TARC were significantly lower in suicide attempters than in healthy controls. Low chemokine levels were specifically associated with psychotic symptoms and pain. In the samples collected at follow-up,

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TARC was significantly lower in suicide attempters compared to psychiatric patients who had never attempted suicide. We also found a positive correlation between blood TARC and brain-derived neurotrophic factor (BDNF) levels. Our study thus provides evidence of reduced chemokine levels in suicide attempters, both in the acute suicidal setting, and at long-term, compared to non-attempters. These results warrant future studies on the detailed neurobiological functions of chemokines in psychiatric patients.
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1. Introduction

Chemokines are small proteins originally described to control the chemotaxis of leukocytes, which is essential for normal functioning of immune system under physiological and pathological conditions (Sallusto and Baggiolini, 2008). Chemokines are also produced by the cells of the central nervous system (CNS), including astrocytes, microglia and neurons (Ambrosini and Aloisi, 2004). In the CNS, chemokines have been shown to regulate neuronal progenitor cell migration, axonal growth and neuronal survival (Rostene et al., 2007). Neuron-derived chemokines modulate calcium transients and glutamate release in astrocytes, as well as migration and activation of microglia, thus playing an important role in the neuron–glia interactions (de Haas et al., 2007). In addition, several studies have indicated that chemokines can affect neuronal activity through modulation of neurotransmission (Gosselin et al., 2005; Skrzydelski et al., 2007).

Not surprisingly, chemokines have been implicated in a number of neurological diseases associated with immune activation and local inflammatory responses including Alzheimer's disease, Parkinson's disease, multiple sclerosis and stroke (Bajetto et al., 2002; Kalkonde et al., 2007). During the last two decades, evidence has emerged supporting a role for inflammation in the pathophysiology of psychiatric disorders as well. Immune alterations are often found in the blood of psychiatric patients (Potvin et al., 2008; Goldstein et al., 2009; Dowlati et al., 2010). Peripherally administered proinflammatory cytokines have been shown to affect behavior (Dantzer et al., 2008) and induce major depressive disorder (MDD) in a subset of patients (Denicoff et al., 1987; Capuron et al., 2009). Several studies have highlighted a possible involvement of inflammation in suicidal behavior. Increased levels of soluble interleukin-2 (IL-2) receptor were initially found in the blood of suicide attempters (Nassberger and Traskman-Bendz, 1993). We have reported high IL-6 and tumor necrosis factor-α (TNF-α) levels in the blood of suicide attempters compared to equally depressed non-suicidal patients (Janelidze et al., 2011). At the same time, the inflammatory changes seem to occur not only in the periphery but also in the CNS. For example, IL-6 levels are increased in the cerebrospinal fluid (CSF) of suicide attempters and correlate with the severity of depressive symptoms (Lindqvist et al., 2009). Furthermore, microgliosis and elevation of cytokine mRNA transcripts have been demonstrated in post-mortem brain tissue from suicide victims (Steiner et al., 2008; Tonelli et al., 2008).

Despite the evidence of immune activation, limited data are available for the role of chemokines in psychiatric disorders. Patients with posttraumatic stress disorder and panic disorder display increased serum levels of MCP-1, MIP-1α and eotaxin (Hoge et al., 2009). Plasma MIP-1β, but not eotaxin-1 or MCP-1, is also elevated in obsessive-compulsive disorder (Fontenelle et al., 2012). High levels of IL-8 in the CSF have been linked to symptoms of alexithymia and anxiety in patients with non-inflammatory neurological disorders (Uher and Bob, 2011). Studies investigating chemokine changes in depression so far produced inconsistent result. Lehto et al. found lower levels of MCP-1, MIP-1β and IL-8 in the blood of depressed patients compared to controls (Lehto et al., 2010). In contrast, two earlier reports had shown increased blood levels of MCP-1 and eotaxin-1 in depressed patients (Sutcigil et al., 2007; Simon et al., 2008). To the best of our knowledge, it has not been examined whether chemokines are altered in suicide attempters. Suicide attempters constitute a group of psychiatric patients with a comparatively well-defined and pronounced symptom; the suicidality, represented by the actual attempt. This clearly distinguishes them from other patients, in spite of being an otherwise heterogeneous group with respect to psychiatric diagnoses. In line with this, neurobiological changes have been found in studies based on suicidal patients (Ernst et al., 2009), and pharmacological trials indicate that the group might be specific in its response to treatments as well (Price et al., 2009). Our primary hypothesis was that as a consequence of a low-grade CNS inflammation, chemokines would be elevated in the CSF. This would be in agreement with previous evidence of elevated cytokines in the CSF and microgliosis in post-mortem brains of suicide victims (Steiner et al., 2008; Lindqvist et al., 2009). However, due to findings indicating that stress may decrease chemokine levels (Kim et al., 1995; Zhou et al., 2007), and clinical evidence of decreased chemokine levels in the blood of depressed patients (Lehto et al., 2010), there was also a possibility that we would find the opposite result, decreased chemokine levels in our patients.

To explore this, we measured eotaxin-1, IP-10, MIP-1β, MCP-1, MCP-4 and TARC in the CSF of a total of 137 suicide attempters and 43 healthy controls in the acute setting after a suicide attempt. The study was designed in a cross-sectional fashion, enrolling all suicide attempters independent of diagnoses. For differences in chemokine levels *within* the suicide attempters we also analyzed the largest diagnostic subgroups enrolled in the study. In order to further understand the relation between chemokines and psychiatric symptoms, we analyzed the association between CSF chemokines and the scores on several well-defined psychiatric rating scales. Two-tailed tests were performed in all cases. Moreover, in order to determine whether chemokine alterations persist beyond suicidal state, we measured chemokine levels in the blood of a subset of the suicide attempters in a long-term Follow-up study, about 12 years after the suicide attempt.

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