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A meta-analysis of chemokines in major depression☆

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ABSTRACT

Chemokines are increasingly recognised as playing a role in depression. Here we meta-analyse the data on concentrations of all chemokines in patients diagnosed with a major depression versus healthy controls. We included studies which utilised Diagnostic and Statistical Manual (DSM)-IV diagnostic criteria for major depression, participants free from major medical conditions, studies with healthy controls, and unstimulated measurements of chemokines. We only included chemokines which had ≥3 studies performed. Two chemokines and 15 studies in total met criteria for this meta-analysis; 8 for Monocyte Chemotactic Protein (MCP)-1/CCL2 (n = 747), and 7 for Interleukin (IL)-8/CXCL8 (n = 560). There were significantly higher concentrations of CCL2/MCP-1 in depressed subjects compared with control subjects – overall mean difference of 36.43 pg/mL (95% CI: 2.43 to 70.42). There was significant heterogeneity across these studies (I2 = 98.5%). The estimates of mean difference between the control and depression groups did not remain significant when the trim-and-fill procedure was used to correct for publication bias. There was no significant difference in concentrations of IL-8/CXCL8 in depressed subjects compared with control subjects. Significant heterogeneity was found across these studies (I2 = 96.7%). The estimates of mean difference between the control and depression groups remained non-significant when the trim-and-fill procedure was used to correct for publication bias. This meta-analysis reports significantly heterogeneity in this field among studies. There are higher concentrations of the chemokine MCP-1/CCL2 in depressed subjects compared with control subjects, and no differences for IL-8/CXCL8. More high quality research and consistent methodologies are needed in this important area of enquiry.

1. Introduction

Novel diagnostic and treatment strategies for depression are urgently needed. Recent global data suggests unipolar depression currently ranks 11th for disability adjusted life years, a 37% increase since 1990 (Murray et al., 2012). The burden is expected to continue to grow into the 21st century (Holtzheimer et al., 2008; Murray et al., 2012). Hence, this is an unprecedented burden of depressive illness requiring increased effort to find novel therapeutic agents for treatment (Licinio, 2011).

In the field of psychiatric immunology, much of the focus on the role of the immune system in depression has been placed on the innate immune response and inflammation. Innate immune cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and interferon (IFN)-γ have been repeatedly shown to exert effects on key processes such as neuroplasticity, neurotransmission, oxidative stress and neuroendocrinological functions that are considered to be central to the development of depression (Dantzer et al., 2008; Eyre and Baune, 2012; Haroon et al., 2012; McAfoose and Baune, 2009; Miller et al., 2009). The seminal meta-analysis (Dowlati et al., 2010) of 24 studies found significantly higher concentrations of the proinflammatory cytokines, TNF-alpha and IL-6, in depressed subjects compared with control subjects. An updated meta-analysis (Haapakoski et al., 2015) of IL-6, C-reactive protein and TNF-α found higher levels of IL-6 and CRP in depressed patients versus controls (29 studies for IL-6 and 20 for CRP). These studies strengthen evidence that depression is accompanied by activation of the inflammatory response system (Dowlati et al., 2010).

An involvement of immune factors in the pathophysiology of depression is now considered to be far greater than that of only the innate immune system, inflammation and glia (Eyre et al., 2015). Indeed, a complex interaction is suspected to occur in the CNS between parts of the innate and adaptive immune system (Ransohoff and Brown, 2012). For example, chemokines are increasingly believed to be involved in depression pathophysiology, likely through neuromodulatory and neurotransmitter-like effects, as well as

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regulation of neurogenesis and axon sprouting (Stuart and Baune, 2014; Stuart et al., 2015).

Recent advances in basic neuroscience have begun to describe novel roles for chemokines in neurobiological processes relevant to depression (Stuart and Baune, 2014; Stuart et al., 2015). In looking beyond traditional roles in chemotaxis of immune cells, these novel processes may include regulating the migration, proliferation, and differentiation of neural stem/progenitor cells; regulation of axon sprouting and elongation; regulating the infiltration and activation states of central and peripheral immune cells; control of blood–brain barrier permeability; regulation of neuroendocrine functions; pre- and post-synaptic modulation of traditional neurotransmitter systems; and possibly direct neurotransmitter-like effects (Reaux-Le Goazigo et al., 2013; Rostene et al., 2011a, 2011b, 2007). For systematic reviews from this group see (Stuart and Baune, 2014; Stuart et al., 2015). The disruption of these functions in vital neurodevelopmental periods or in later life may be mechanistically relevant to the pathogenesis and pathophysiology of depression, while restoration of homeostasis in these functions may be relevant to recovery (Stuart and Baune, 2014; Stuart et al., 2015). From a clinical study perspective, we are aware of a number of cross-sectional studies (monocyte chemoattractant protein (MCP)-1/CCL2 (Domenici et al., 2010; Grassi-Oliveira et al., 2012; Jonsdottir et al., 2009; Lehto et al., 2010; Shen et al., 2010; Suarez et al., 2004; Sutcigil et al., 2007) (Bai et al., 2014; Carvalho et al., 2014; Motivala et al., 2005; Piletz et al., 2009; Simon et al., 2008); macrophage inflammatory protein (MIP)-1α/CCL3 (Merendino et al., 2004; Suarez et al., 2004); CXCL1 (Lee et al., 2009; Merendino et al., 2004); IL-8/CXCL8 (Baune et al., 2012a; Domenici et al., 2010; Jonsdottir et al., 2009; Marsland et al., 2007; O'Brien et al., 2007; Podlipny et al., 2010; Suarez et al., 2004) (Carvalho et al., 2014; Hallberg et al., 2010; Hocaoglu et al., 2012; Lehto et al., 2010; Simon et al., 2008; Song et al., 1998); MCP-3 (Lee et al., 2009); TNF-β (Lee et al., 2009); IL-16 (Lee et al., 2009); CTACK (Lee et al., 2009); macrophages migration inhibitory factor (MIF) (Lee et al., 2009); CCL11 (Grassi-Oliveira et al., 2012; Magalhaes et al., 2014); CXCL11/I-TAC (Lu et al., 2013); MEC/CCL28 (Lu et al., 2013); TECK/CCL25 (Lu et al., 2013); Interferon gamma-induced protein (IP)-10/CXCL10 (Simon et al., 2008; Wong et al., 2008); RANTES/CCL5 (Grassi-Oliveira et al., 2012; Shen et al., 2010). There are only two prospective studies exploring associations between chemokines and depression (Baune et al., 2012b; Eller et al., 2008). In one study, the associations between serum CXCL8 (IL-8) and depressive symptoms were explored in a large cohort of population-based, elderly participants for two years (age 70–90 years) (Baune et al., 2012b). Results indicated that serum IL-8/CXCL8 was positively associated with depressive symptoms on the geriatric depression scale (GDS) at baseline ($P = 0.025$), at two years follow-up ($P = 0.038$), and an increase in depressive symptoms from baseline to two years ($P = 0.021$). Further prospective research, across age groups, is required to understand the role of chemokines as biomarkers and neurobiological factors in depression.

The association between chemokine dysfunction and depression has been documented in individual studies of various chemokines, however the association is not consistently significant in all studies or for all chemokines. Thus a generalizable pattern of chemokine dysfunction in depression remains to be defined. Fortunately the results from individual studies can be combined quantitatively using meta-analytical techniques to improve the strength of the evidence. Taken together, this study reports the results of a meta-analysis conducted to determine whether the concentrations of specific cytokines differs quantitatively between patients diagnosed with a major depressive episode and control subjects.

2. Methods and materials

2.1. Data sources

We (AP and JJ) searched Embase, PsycINFO, Ovid Medline, ScienceDirect, Google Scholar and the Cochrane Central Register of Controlled Trials database up to September 2015. We also manually scrutinized references cited in the systematically searched articles. To optimize sensitivity in searching clinical studies, we used the following basic terms: XCL*, CX3C*, CCL*, CXCL*, IL-*, MCP, scya, scyb, NAP, GCP, depression, major depressive disorder and depressive symptoms.

2.2. Study selection

Studies were selected for data extraction and analysis based on the following inclusion criteria: (a) original research studies measuring chemokine concentrations in depressed and non-depressed subjects; (b) subjects met DSM-IV criteria for major depression; (c) studies were in English; (d) participants were free from major medical comorbidities (e.g. cancer, heart disease, arthritis); (e) psychiatrically healthy subjects were used as controls; (f) unstimulated chemokine analyses were used. We excluded studies including participants with stimulated chemokine-based analyses or non-serum/plasma markers.

2.3. Data extraction

Two independent reviewers (AP and JJ) used a custom data extraction template to summarize the selected articles. Abstracted information included age, gender, sample size, depression metrics, comorbidities, chemokines analysed, method and source, and concomitant drug use. Where possible, we also sought key data that were missing from the original reports through correspondence with the investigators.

2.4. Quality assessment

This meta-analysis was carried out according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (Liberati et al., 2009). We used the Newcastle-Ottawa Quality Assessment Scale (Hartling et al., 2013) for observational studies to assess quality; this scale is recommended by the Cochrane Collaboration. With this method, each study can obtain a maximum of 9 points in three categories: *selection* of study participants (adequate definition, validation and representativeness of cases and controls), *comparability* of cases and controls, and the ascertainment of *exposure*. For this study, our quality points for exposure were adapted from Haapakoski et al. (Haapakoski et al., 2015). These included method of assay, consistency of assay used, three or more immune markers analysed. Given the small number of studies in this field, we included all in our meta-analysis (see Table 1).

2.5. Statistical analysis

Weighted mean differences between controls and cases were used to calculate the effect size (ES) of each study. A spreadsheet containing the extracted study data and the calculated ES was imported into Stata 12.0 (StataCorp. 2011. *Stata Statistical Software*: *Release 12*. College

Table 1
Quality assessment of studies included in the meta-analysis.

Study	Selection	Comparability	Exposure	Total
Song et al. (1998)	*	*	***	5
Motivala et al. (2005)	***	**	**	7
O'Brien et al. (2007)	**		***	5
Sutcigil et al. (2007)	**	*	***	6
Simon et al. (2008)	**	*	**	5
Eller et al. (2008)	**	*	***	6
Jonsdottir et al. (2009)	**	**	***	7
Piletz et al. (2009)	***	*	**	6
Lehto et al. (2010)	***	*	***	7
Hocaoglu et al. (2012)	**	**	***	7
Bai et al. (2014)	**	**	***	7
Carvalho et al. (2014)	***	**	**	7