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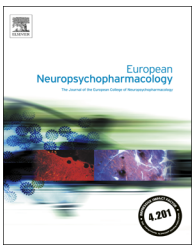

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The role of inflammatory cytokines in suicidal behavior: A systematic review

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Abstract
There is growing evidence that inflammatory mediators play a critical role in the pathophysiology of both major depression and suicidal behavior. Immunological differences have been reported in both major affective disorders and suicidal behavior. Specifically, increased levels of pro-inflammatory cytokines have been shown to correlate with the severity of depression and various cytokines have been identified as potentially important in understanding the pathophysiology of major affective disorders/suicidality. We aimed to conduct a systematic review of the current literature to investigate the association between inflammatory cytokines and suicidal behavior. Only articles from peer-reviewed journals were selected for inclusion in the present review. Most studies documented the association between suicidality and IL2, IL-6, IL-8, TNF-α and VEGF levels that have been found altered in suicidal behavior. The presence of major depressive disorder (MDD) with suicidal ideation/attempts was associated with differences in inflammatory cytokine profile when compared to that without suicidal ideation/attempts. Most suicide attempters or subjects with suicidal ideation showed an imbalance of the immune system but this does not imply the existence of a causal link. Also, not all studies demonstrated a positive correlation between inflammatory cytokines and suicidal behavior. Further additional studies should elucidate the molecular mechanisms of the immune activation pathways underlying suicidality.

1. Introduction

Major depressive disorder (MDD) is a chronic and invalidating illness that is responsible for significant functional impairment and leads to both social and occupational disability (Réka et al., 2012; Skolnick et al., 2009). Patients

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with MDD commonly experience long-term negative outcomes, frequent relapses, incomplete recovery between episodes, and persistent psychosocial impairment (Greer et al., 2010). MDD is considered one of the 10 leading causes of disability affecting the global population (Lopez et al., 2006) and is associated with multiple chronic medical illnesses (McIntyre et al., 2012) and a profound disability although many psychopharmacological agents are currently available for its treatment (Serafini et al., 2013). MDD is also associated with an increased risk for suicidal behaviors (Pompili et al., 2011, 2012a, 2012b; Serafini et al., 2011, 2012, 2013; Innamorati et al., 2011). However, our current knowledge concerning the neurobiology of suicide is still limited.

Immunological differences have been associated with both major affective disorders and suicidal behaviors. Inflammatory mediators and oxidative stress leading to excitotoxicity may play a critical role in the pathophysiology of major depression. Several cytokines have been identified as potentially important in understanding the pathophysiology of mood disorders and suicidality. An imbalance among pro-inflammatory (Interleukin IL-1b (IL-1b), IL-2, IL-6, interferon-gamma (IFN-γ), and tumor-necrosis Factor-alpha (TNF-α)) (Ackerman et al., 1998; Maes, 1995, 1999, 2011) and anti-inflammatory cytokines (IL-4 and IL-10) has been reported in untreated depressed patients. Moreover, increased levels of pro-inflammatory cytokines correlate with the severity of depression (Isung et al., 2012a, 2012b; Kim et al., 2008; Anisman and Merali, 2003; Kim and Maes, 2003). Also, immune abnormalities such as activation of the inflammatory response system, increased levels of pro-inflammatory cytokines, increases in prostaglandin E2 and negative immunoregulatory cytokines in peripheral blood are frequent in MDD (Maes, 1999; Kim et al., 2002; Leonard, 2001). As a result, MDD resulted usually associated with several somatic diseases. This association has been reported to be bi-directional as not only poor physical health predicted an increased risk of future depression independently of previous depressive episodes and demographic covariates but also major depression predicted an increased risk of future poor physical health independently of previous physical health and demographic covariates (Cohen et al., 1998). Also, various immunomodulatory medications may be used for the treatment of several underrecognized symptoms such as pain, muscle spasms, fatigue, severe depression, sexual dysfunction, bladder and bowel dysfunctions (Krupp and Rizvi, 2002). Potential exacerbations of the illness during the postpartum period may be managed using immunomodulatory therapy soon after delivery (Achiron et al., 2004).

A link between inflammation, major depression and suicide has also been demonstrated by the fact that the treatment of patients with hepatitis C increases risks for both depression and suicidal attempts (Dieperink et al., 2004; Kraus et al., 2003; Capuron et al., 2002). Sockalingam and Abbey (2009) suggested that antidepressant pretreatment is beneficial for patients with increased baseline depressive symptoms and a history of IFN-alpha-MDD. Studies reported that depressive symptoms secondary to IFN-alpha may be successfully treated with selective serotonin reuptake inhibitors (SSRIs) although limited evidence are available.

Interestingly, some antidepressant drugs appear to have anti-inflammatory properties possibly because they reduce the release of proinflammatory cytokines, increase the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 or inhibit cyclo-oxygenase (Colin et al., 2003).

Recent evidence implicate vascular endothelial growth factor (VEGF) and kynurenine levels in the pathophysiology of suicidality (Isung et al., 2012a, 2012b; Sublette et al., 2011). Iga et al. (2007) reported that the higher expression levels of VEGF mRNA in the peripheral leukocytes were associated with the depressive state of 32 patients with MDD compared with 32 age- and sex-matched controls and the recovery after 8-week treatment with paroxetine was associated with a significant clinical improvement. Baseline levels of peripheral VEGF may predict treatment response in patients with MDD (Halmai et al., 2013). Inadequate responses to antidepressant treatment as well as abnormal VEGF expression have been commonly associated with impairments of cAMP-CREB signaling pathways. The authors concluded that understanding the molecular mechanisms of treatment response may provide new strategies for treatment-resistant patients in order to reduce negative outcomes such as suicidal behavior.

Individuals with MDD and suicidal ideation may also have higher peripheral inflammatory chemokine levels when compared to those without suicidal ideation (Grassi-Oliveira et al., 2012). Other findings suggest that suicidal patients display a distinct peripheral blood cytokine profile compared to non-suicidal patients with depression (Kim et al., 2008; Janelidze et al., 2011).

Considering this background, we aimed to systematically review the current literature concerning the association between inflammatory or pro-inflammatory cytokines and suicidal behavior.

2. Experimental procedures

2.1. Information sources, search strategy and study selection

A detailed search strategy summarized in Figure 1 was used to identify relevant studies. In order to provide a new and timely critical review of inflammatory and pro-inflammatory cytokines and their possible involvement in suicide we performed a detailed Pubmed/Medline, Scopus, Science Direct, PsycLit, PsycInfo search to identify all papers and book chapters in English language during the period between 1980 and January 2013.

The search used a combination of the following terms: “Inflammation” AND “Inflammatory Cytokines” OR “pro-inflammatory cytokines” AND “Suicid*” (including suicidal behaviors OR suicide ideation OR suicidal thoughts OR deliberate self harm OR suicidal attempts). Where a title or abstract seemed to describe a study eligible for inclusion, the full article was examined to assess its relevance based on the inclusion criteria. Two independent researchers (GS, MP) conducted a two-step literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with two senior authors (WC, PG). The reference lists of the articles included in the review were also manually checked for relevant studies (SME, HS, MP). All English language full-text articles reporting original data about the main topic were included.