Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

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

Review article

Examining the role of neuroinflammation in major depression

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ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form
12 May 2015
Accepted 8 June 2015

Keywords:
Major depression
Inflammation
Hypothalamic pituitary adrenal axis
Tumor necrosis factor
Interleukin

ABSTRACT

Recent findings have established a connection between inflammation and major depression and specifically the role of the hypothalamic–pituitary–adrenal (HPA) axis in depression. This article reviews clinical and experimental studies examining the role of the HPA axis, HPA hyperactivity (resulting in increased cortisol levels), as well as the proinflammatory cytokines tumor necrosis factor, C-reactive protein, and the interleukins, in depressed patients. Similarly this paper will review data supporting increased cytokine levels in depression and specifically differential effects in treatment-resistant patients, as well as potentially distinguishing in particular depression subtypes. Understanding the role of the immune system and inflammation in patients with major depression is essential in order to develop efficacious treatments potentially targeting inflammation in relation to the depression in order to reduce patient symptomatology and comorbidities.

Contents

1. Introduction

The prevalence of mental health disorders continues to rise worldwide, such that it is estimated that 1 in 4 individuals will be affected by a mental health disorder at some point in their lifetime (World Health Organization, 2011). Research has found that the most prevalent mental health disorders are depressive and anxiety disorders (Kessler et al., 2012), both of which hinder an individual's functioning on multiple domains.

Depression is estimated to significantly impact 350 million people worldwide and it is projected to become the primary cause of global disease burden by 2030 (World Health Organization, 2012). Furthermore, the Global Burden of Disease Study found that

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http://dx.doi.org/10.1016/j.psychres.2015.06.009
0165-1781/

depressive disorders were the second leading cause of Years Lived with Disability (YLDs) and the leading cause of Disability Adjusted Life Years (DALYs) globally (Ferrari et al., 2013). Depressive disorders, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (American Psychiatric Association, 2000), include Major Depressive Disorder (MDD) and Dysthymia. MDD is characterized by Major Depressive Episodes (MDE) that are symptomatic almost all day, every day for periods of at very least 2 weeks, whereas dysthymia is described as a milder but more chronic form of depression lasting for at least 2 years (Ferrari et al., 2013). Changes with the DSM-5 (American Psychiatric Association, 2013), have included the insertion of Persistent Depressive Disorder (that includes both Dysthymia, and chronic and unremitted Major Depressive Disorder), as well as including a variety of specifiers, such as "with anxious distress," in which the presence of anxiety symptoms suggests potentially higher risks of complications in diagnosis, as well as a higher likelihood of chronicity (Lamers et al., 2011).

With medical comorbidities being very common in MDD, growing interest has been placed on the role of the immune system and inflammation and its relation to psychiatric disorders. Although it has generally been said that genetic and environmental factors may play a significant role in the cause of depression (Lesch, 2004), recent research has focused on the role of cytokines and immune biomarkers (Felger and Lotrich, 2013) as predictors of the disorder. The present commentary will review the current scientific literature in regard to immune mediated theories in depression.

2. Methods

The present review is aimed at evaluating and interpreting literature regarding depressive disorders and the role of the immune system, specifically, HPA activity and a variety of inflammatory cytokines. A PubMed, MEDLINE, and PsycINFO literature search was performed for the past decade (2004 to 2014), for clinical studies in depressed patients assessing the role of the immune system. Keywords for this review included: major depression, immune system, inflammation, cytokines, TNF, interleukin, cortisol, and HPA activity. Participants in the included studies were a minimum of 18 years and there was no upper age limit, in order to include studies of late-onset depression. Included studies utilized patients that were clinically diagnosed with a depressive disorder through the use of a structured interview and/or physician assessment and excluded studies relying solely on psychometric scores for diagnoses. Titles and abstracts of articles were reviewed in order to determine inclusion/exclusion criteria, and full manuscripts were read when titles and/or abstracts were unclear.

3. The immune system and cytokines

The role of cytokines can be understood simply as hormonal messengers responsible for most of the biological effects in the immune system. They can be functionally divided into two groups: those that are proinflammatory and those, which are essentially anti-inflammatory, but may also promote allergic or autoimmune responses.

Lymphocytes (the primary cells of the immune response) are of two types, the T and B lymphocytes, both of which specifically tailor their responses to each pathogenic insult as part of the adaptive immune system. During an infection, activation of the B cells causes them to proliferate, differentiate, and synthesize a variety of potential antibodies to specific pathogenic antigens (Mosmann and Coffman, 1989). Immunological responses also activate T cells, inducing them to differentiate into a wide variety of subtypes, including cytotoxic T cells and T helper cells. Cytotoxic T cells recognize and destroy infected cells, and T helper cells communicate with B cells to mediate appropriate immune responses (Mosmann and Coffman, 1989). Changes in gene expression and epigenetic regulation play a large part in T and B cell activation mechanisms (Mosmann and Coffman, 1989), but with dysregulation of this system in either, or both T or B cell function, a resulting immunodeficiency or alternatively autoimmune illnesses can occur.

The major source of cytokines is the T lymphocyte, which bears antigen specific receptors on their cell surface in order to facilitate recognition of foreign pathogens. They can also recognize normal tissue in order to limit the development of autoimmune diseases. T lymphocytes can be separated into two main subtypes by the presence of specific cell surface molecules known as CD4 and CD8. The T lymphocytes expressing CD8 are broadly known as Cytotoxic T cells (or Killer T cells), which act to destroy cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways (Iannacone et al., 2005; Milstein et al., 2011). If the T-cell receptor (TCR) is specific for that antigen, it binds to the complex of the major histocompatibility complex (MHC) class I molecule and the antigen, and the T cell destroys the cell.

In contrast, the T lymphocytes expressing CD4 are known as helper T cells, which function as prolific cytokine producers. The helper T cells can be further subdivided into Th1 and Th2 (with the cytokines they produce known respectively as Th1-type cytokines and Th2-type cytokines) (Berger, 2000; Romagnani, 2000). The Th1-type cytokines, for example Interferon-γ (IFN-γ), tend to modulate the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. As such, excessive Th1-type cytokines can lead to proinflammatory responses and therefore uncontrolled tissue damage (Berger, 2000; Romagnani, 2000).

The Th2-type cytokines, including interleukins 4, 5, and 13, are associated with the promotion of immunoglobulin E (IgE) and eosinophilic responses in atopy (Berger, 2000; Romagnani, 2000). Interleukin-10 is also a Th2-type cytokine, but functions primarily in the anti-inflammatory response (Berger, 2000; Romagnani, 2000). In excess, Th2 responses will counteract the Th1 mediated microbicidal action (Berger, 2000; Romagnani, 2000). Thus, the optimal scenario in humans would therefore seem to be well-balanced Th1 and Th2 responses, ideally varying in order to suit the specific immune challenges faced at that specific time.

As the relative Th2 imbalance is thought to result in allergies, immunologists have been attempting to redirect allergic Th2 responses in favour of Th1 responses with the hopes of reducing atopic incidence (Berger, 2000).

Levels of tumor necrosis factor (TNF), which is a cytokine produced largely by macrophages to regulate immune cells as well as induce apoptosis (Wajant et al., 2003) has also been implicated in depression. TNF has the ability to exert its function through the binding to one of two receptors, TNF-receptor type 1 (TNF-R1) or TNF-receptor type 2 (TNF-R2). TNF-R1 is expressed in most bodily tissues, whereas TNF-R2 is located primarily in immune cells, associated with the lymphatic system (Wajant et al., 2003).

TNF regulated activities generally act together via interleukin-6 (IL-6), which is usually secreted by T cells and macrophages during infection (Simpson et al., 1997). As a result, IL-6 induced repression of brain-derived neurotrophic factor (BDNF) has been implicated in the development of major depressive disorder (Sharma et al., 2008), and directly resulting in altered neural connectivity and alterations in the emotional responses (Somerville et al., 2006) and therefore the typical depressive symptomatology of MDD.

4. Immune mediators in major depressive disorder

4.1. Cortisol and the HPA axis

Major Depressive Disorder (MDD) is a severely debilitating disorder that imposes a significant burden on one's quality of life.

Please cite this article as: Furtado, M., Katzman, M.A., Examining the role of neuroinflammation in major depression. Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.06.009