Psychiatry Research 229 (2015) 37–48

Contents lists available at ScienceDirect

Psychiatry Research

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

Review article

Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders

Melissa Furtado [a], Martin A. Katzman [a,b,c,d,e,*]

[a] START Clinic for Mood and Anxiety Disorders, Toronto, Ontario, Canada
[b] Department of Psychiatry, Faculty of Medicine, University of Toronto, Ontario, Canada
[c] The Northern Ontario School of Medicine, Thunder Bay, Ontario, Canada
[d] Department of Psychology, Lakehead University, Thunder Bay, Ontario, Canada
[e] Adler Graduate Professional School, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form
27 May 2015
Accepted 29 May 2015
Available online 6 June 2015

Keywords:
Generalized anxiety disorder
Social anxiety disorder
Panic disorder
Posttraumatic stress disorder
Obsessive compulsive disorder
Inflammation
Hypothalamic pituitary adrenal axis

ABSTRACT

As prevalence of anxiety, posttraumatic stress, and obsessive compulsive disorders continue to rise worldwide, increasing focus has been placed on immune mediated theories in understanding the underlying mechanisms of these disorders. Associations between the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and these disorders have been recognized in the scientific literature, specifically in regard to cortisol levels, as well as changes in pro- and anti-inflammatory cytokines. The present commentary will systematically assess the scientific literature within the past decade in regard to the psychoneuroimmunology of anxiety, posttraumatic stress, and obsessive compulsive disorders. Understanding the mechanisms of these disorders is essential in order to determine efficacious and targeted treatment strategies, which may lead to substantial improvements in overall functioning, as well as significant decreases in societal and economic burden.

Contents

1. Introduction

Anxiety disorders as described by early formulations of the Diagnostic and Statistical Manual of Mental Disorders (DSM) up to DSM IV TR, included generalized anxiety disorder (GAD), social anxiety disorder (SAD) specific phobia (SP), and panic disorder (PD), as well as (PTSD) and obsessive compulsive disorder (OCD). Changes associated with the development of DSM 5 now

* Corresponding author at: START Clinic for Mood and Anxiety Disorders, 32 Park Road, Toronto, Ontario, Canada M4W 2N4. Tel.: +1 416 598 9344; fax: +1 416 598 8198.
E-mail address: mkatzman@startclinic.ca (M.A. Katzman).

http://dx.doi.org/10.1016/j.psychres.2015.05.036
0165-1781/

categorize PTSD and OCD within Trauma- and Stressor-Related Disorders and Obsessive-Compulsive and Related Disorders, respectively, rather than as anxiety disorders (American Psychiatric Association, 2013). Additionally, judgment of one's social fears characterized as being excessive or unreasonable in the diagnostic criteria for SAD has been switched from patient to clinician. This change has been made in order to take the burden off the patient in terms of recognizing their fears as excessive. As the literature has suggested that the ratio of generalized to nongeneralized SAD is as high as 3:1 (Lydiard, 2001), there has been a replacement of the *generalized* specifier with the *performance only* specifier in the DSM 5 (American Psychiatric Association, 2013). This allows for the generalized form of the social anxiety disorder diagnosis to be the "regular or general form," with rarer forms, which are only experienced in performance situations such as public speaking, called out by the performance specifier.

These disorders, which often originate early in life (Kessler et al., 2007), have been found to have lifetime prevalence rates as high as 28.3% globally (Baxter et al., 2013) and result in high economic costs at least in part, as an effect of the extensive utilization of primary care services (Kessler and Greenberg, 2002). In fact, it has been estimated that the annual cost of anxiety disorders in the United States is $42 billion (Greenberg et al., 1999), much of which is most likely due to misdiagnosis and inappropriate treatment. Understanding the causes of these disorders is therefore crucial in order to decrease costs and enhance patient outcome.

Heightened interest has recently been placed on psychoneuroimmunology research, specifically in regard to anxiety disorders, as well as PTSD and OCD. These patients have been found to have an increased risk of comorbid neurological, vascular, respiratory, and metabolic conditions (Sareen et al., 2005; Buist-Bouwman et al., 2006). While relatively much more has been published in the depression literature (Young et al., 2004; Thomas et al., 2005; Fitzgerald et al., 2006; Pavón et al., 2006; Pasco et al., 2010; Hinkelmann et al., 2012; Vogelzangs et al., 2012; Krogh et al., 2014; Powell et al., 2013; Raison et al., 2013; Wium-Andersen et al., 2013; Köhler et al., 2014; Udina et al., 2014), significant work is required to understand the interaction between the anxiety disorders and the neuroinflammatory system. Additionally, individuals with anxiety disorders often experience increased disability when suffering from a comorbid physical condition compared to individuals suffering from the physical condition alone (Sareen et al., 2005; Buist-Bouwman et al., 2006), therefore resulting in decreased quality of life.

The present commentary will comprehensively review scientific literature from the past decade, specifically related to psychoneuroimmunology in anxiety, posttraumatic stress, and obsessive compulsive disorders.

2. Methods

The present comprehensive review evaluates the current scientific literature in anxiety, posttraumatic stress, and obsessive compulsive disorders, specifically in terms of the particular role of neuroinflammation and biomarkers in the anxiety and anxiety related disorders. Focus is placed on the role of the hypothalamic–pituitary–adrenal (HPA) axis, as well as pro- and anti-inflammatory cytokines. In order to establish a complete review, a literature search across PubMED, PsycINFO, and MEDLINE was performed for scientific research studies published in the previous ten years (2004–2014). Keywords for this search included: anxiety disorders, generalized anxiety, social anxiety, panic disorder, posttraumatic stress disorder, obsessive compulsive disorder, HPA axis, inflammation, cytokines, cortisol, interleukins, and immune system. Studies included patients with clinical diagnoses of anxiety disorders, PTSD, or OCD. An age limit for participants in the reviewed studies was not employed, in order to include studies in child, adolescent, adult, and elderly populations.

3. Psychoneuroimmunology and cytokines

Immunological and molecular research techniques have steadily increased in terms of their use in assessing psychiatric populations, as associations between pro- and anti-inflammatory biomarkers have been established.

During stressful events, the HPA axis is activated as a result of corticotropin releasing hormone (CRH) secretion, as well as arginine vasopressin (AVP), which stimulate the release of adrenocorticotropic hormone (ACTH) (Faravelli et al., 2012). ACTH stimulates the release of glucocorticoids, and specifically cortisol, from the adrenal cortex (Faravelli et al., 2012).

Cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL) 2 and 6, mediate information between the central nervous system (CNS) and peripheral immune system (Kasper et al., 2003). Furthermore, they have the ability to initiate the production of other cytokines. Cytokines within the CNS may play a variety of roles, including but not limited to, initiating immune processes such as allergic response, involvement in repair mechanisms following injury, and regulation of the endocrine system via the HPA axis (Kasper et al., 2003).

T-helper cells, which are subdivided based upon the cytokines they produce, into Th1 cells [secreting cytokines IL-2, TNF-α and interferon-γ (IFN-γ)] and Th2 cells (secreting cytokines IL-4, 5, 6, 10, 13), function primarily to activate cell-mediated and humoral immunity, respectively (Glik and Douvdevani, 2006). In psychiatric disorders, such as anxiety, PTSD, and OCD, the balance between Th1 and Th2 cytokines is often altered.

Specifically, these disorders are often associated with a shift in Th1/Th2 balance to Th2 dominance, such that IL-6 (secreted by Th2 cells) and TNF-α (necessary for the induction of Th2 responses) are typically increased (Martino et al., 2012). Furthermore, deficits in serotonergic activity may be related to decreased Th1 cytokines with a shift towards Th2 (Fernandez and Gaspar, 2012), which results in the onset of anxious symptoms.

3.1. Psychoneuroimmunology in anxiety disorders

Anxiety disorders are often comorbid with medical conditions such as cardiovascular disease, diabetes, and autoimmune disorders such as rheumatoid arthritis. Disability is increased when anxiety disorders are present in combination with the medical condition, as compared with the situation when the medical condition is present alone (Sareen et al., 2005). Patients with rheumatoid arthritis (RA) exhibit significantly increased levels of IL-17, TNF-α, and IL-6 compared to healthy individuals. However, RA patients with comorbid clinical anxiety exhibit greater significant increases in IL-17, and these levels have been shown to be positively and independently correlated with anxiety severity (Liu et al., 2012).

Recent research has placed an increased focus on assessing the role of the immune system in psychiatric disorders in order to better understand the underlying mechanisms behind these disorders. Scientific findings may lead to the development of efficacious treatments targeted at these associated biomarkers in various study populations, including children, adolescents, adults, and the elderly.

3.1.1. Generalized Anxiety Disorder

Generalized Anxiety Disorder (GAD) is characterized as excessive worry lasting a minimum of six months (American Psychiatric Association, 2013) often related to routine activities such as health, relationships, work and finances.

In regard to T-cell profiles, statistically decreased T-cell proliferation has been found in GAD patients compared to controls