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Review

Autoantibodies and depression Evidence for a causal link?

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ABSTRACT

Depression is a leading contributor to the global burden of diseases. Despite advances in research, challenges still exist in managing this disorder. Sufferers of autoimmune diseases are often observed to suffer from depression more often than healthy individuals, an association that cannot be completely accounted for by the impact of the disease on the individual. An association between autoimmunity and depressive symptoms also appears to exist in populations with subclinical symptoms. Moreover, researchers have successfully developed murine models illustrating the ability of autoantibodies to induce depressive-like symptoms. This paper will provide an overview of the association between autoantibodies and occurrence of depressive symptoms. Though current evidence appears to support a role for autoantibodies in the pathogenesis of depression, the majority of studies have examined this relationship cross-sectionally, therefore failing to establish a temporal association. Nonetheless, this novel theory meshes with older and newer neurochemical theories of depression. A better understanding of the immuno-pathogenesis underlying depression presents opportunities for more targeted treatment approaches and more timely and appropriate measures of detection.

Contents

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1. Introduction

Depression is the most commonly observed mood disorder, currently estimated to affect 350 million people worldwide (WHO, 2012). Depressive symptoms may be mild, moderate or severe and particular symptoms often cluster to form subtypes of depression (APA, 2000). Currently the most established theory that has been proposed to account for the emergence of depression is the monoamine theory. The latter theory postulates that depression is a result of disturbances in monoaminergic signalling pathways (Elhwuegi, 2004). Over the past several decades however, several compelling non-monoaminergic theories have emerged, that have placed a greater emphasis on glutamatergic neurotransmission (Kugaya and Sanacora, 2005; Palucha and Pilc, 2005), neurogenesis (Dunman et al., 1997) and inflammation (Smith, 1991). Of these 'newer' theories of depression, inflammation is the biological process mostly linked to the occurrence of depression within the current literature (Walker, 2013). While there is now compelling literature to suggest that disturbances in inflammatory signalling contribute to disturbances in mood state it remains unclear what is the primary mechanism responsible for initiating this phenomena. In examining the mechanisms responsible for stimulating an inflammatory response in depression, scientists observed a role for autoantibodies in the pathogenesis of depression. In the current review we will outline the case for autoantibodies as pathologic factors playing both an indirect and direct role in the development of depression.

2. Autoantibody mediated inflammation and depression

2.1. Inflammatory hypothesis of depression

In the 1990s scientists began to notice a relationship between immune dysregulation marked by inflammation and the development of depression (Smith, 1991). Smith ascertained that when patients suffering from cancer in the absence of depression were administered pro-inflammatory (PI) cytokines (McDonald et al., 1987; Niiranen et al., 1988; Spriggs et al., 1988) they were often observed to thereafter develop clinical depression. Moreover, he noted that depressive symptoms often ceased once patients discontinued PI cytokine treatment (Niiranen et al., 1988). This inflammatory hypothesis of depression explained the co-occurrence of depression alongside diseases such as cardiovascular disease and autoimmune disease. However, despite Smith's contribution, the role of PI cytokines in depressive pathology only became increasingly noted following early studies by Maes and colleagues (Maes, 1993, 1995; Maes et al., 1995).

Coinciding with Smith's deductions, researchers were gaining a better understanding of the mechanisms underlying illness-induced behavioural changes also referred to as 'sickness behaviour'. Hart observed mammals infected with a virus or bacteria often exhibited a cluster of behaviours including but not confined to inactivity, lethargy, weakness, sleepiness, loss of appetite, reduced food intake, diminished thirst as well as poor grooming (Hart, 1987). Later this collection of behaviours was widened to include anhedonia, reduced attention and working memory impairment (Yimriya et al., 2000).

In 1992, sickness behaviour was first linked to the action of PI cytokines. Kent et al. (1992) observed a decrease in food seeking behaviour in animals following a challenge with PI cytokine Interleukin-1 (IL-1). The latter behaviour was then reversed following direct injection of the IL-1 receptor antagonist (IL-1a) into the brain (Kent et al., 1992). Building on these findings, in 1996 Yirmiya proposed that the emergence of sickness behaviour and depression shared the same underlying mechanisms (Yirmiya, 1996). Subsequent studies demonstrated that infection with lipopolysaccharide (LPS), a potent PI stimulator, successfully brought about a negative mood in healthy male volunteers no more than four hours following administration (Reichenberg et al., 2001). Moreover, researchers successfully identified particular markers of inflammatory disturbance linked to depression. C reactive protein (CRP), tumour necrosis factor a (TNF-a) and interleukin-6 (IL-6) have been repeatedly recognised to be elevated in depression (Bankier et al., 2009; Danner et al., 2003; Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012; Matthews et al., 2010; Pikhart et al., 2009; Stewart et al., 2009). In addition, individuals suffering from depressive disorder have been observed to possess PI cytokine polymorphisms that subsequently makes these individuals susceptible to exaggerated inflammatory responses (Baune et al., 2010; Cerri et al., 2009, 2010; Clerici et al., 2009; Galecki et al., 2010; Hong et al., 2005; Hwang et al., 2009; Wong et al., 2008).

2.2. Neuro-inflammatory theories of depression

If peripheral inflammation is indeed a driving force in the pathogenesis of depression, it seems likely that these immune markers somehow exert their effect on the central nervous system (CNS). Post-mortem studies of people with depression have proven beneficial in illustrating the ability of PI cytokines to influence the CNS. One particular study observed up-regulated expression of mRNA of PI cytokines in the brains of major depressive sufferers (Shelton et al., 2011). Moreover post-mortem cell counting studies coupled with magnetic resonance imaging and positron emission tomography studies have noted the evidence of prolonged neuroinflammation (significant cell loss) in brains of patients with recurrent depression (Campbell and MacQueen, 2006; Koolschijn et al., 2009; Rajkowska, 2002). These observations collectively birthed the various neuroinflammatory theories of depression (Maes et al., 2009; Muller and Schwarz, 2007). On one hand, it