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Review

The role of macrophages in anti-inflammatory activity of antidepressant drugs

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ABSTRACT

Depression is a common disease influencing patients' quality of life, whose etiology involves complex interactions of environmental, genetic and immunological factors. The latter factors include proinflammatory activation of monocytes and macrophages and increased serum levels of proinflammatory cytokines, altogether formulated as the "macrophage theory of depression". Our current review summarizes the impact of the most commonly used antidepressant drugs on the immune response with special emphasis on the role of macrophages in the clinically observed effects. The anti-inflammatory action of antidepressants mainly results from their direct interaction with immune cells and from changes in the concentration and the relations of neurotransmitters sensed by these cells. The summarized data revealed that Mφs are one of the leading cell populations involved in drug-mediated immune effects that can be observed both in subjects with depression as well as in individuals not suffering from depression. Thus, currently reviewed immunomodulatory effects of the experimental use of different antidepressant drugs suggest the possibility of utilizing them in complex therapeutic strategies dedicated to various inflammatory and immune-mediated diseases. It is worth noting that an excessive inflammatory reaction is also associated with the pathogenesis of various cardiovascular, metabolic and neuro-endocrine diseases. Thus, the inclusion of antidepressants in the complex therapy of these disorders may have beneficial effects through the enhancement of the mood of the patient and alleviation of chronic inflammation. On the other hand, presented data suggest that the influence of chronically used antidepressants on anti-microbial and anti-tumor immunity could also be taken into consideration.

Contents

Abbreviations: Mφs, macrophages; MAO-A, monoamine oxidase-A; SNRI, serotonin-norepinephrine re-uptake inhibitors; SSRI, selective serotonin re-uptake inhibitors; TCA, tricyclic antidepressant drugs.

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1. Introduction

Depression is a common, recurrent disease, which significantly influences the quality of a patient's life, and is ranked by the World Health Organization as the 4th leading cause of disability worldwide (Kessler and Bromet, 2013). The etiology of a major depressive disorder is not yet completely understood and seems to involve complex interactions of environmental, genetic and immunological factors. The latter factors are suspected to include the proinflammatory activation of peripheral monocytes, macrophages (Mφs) and resident brain microglia along with increased serum levels of proinflammatory cytokines, especially those of Mφ origin, both already reported in patients with depression (Beumer et al., 2012; Stelzhammer et al., 2014). The persistence of elevated levels of proinflammatory cytokines was even suggested to be a useful marker to predict the onset of a depressive episode (Raedler, 2011) or the lack of patient response to antidepressant therapy (Eller et al., 2008; Lanquillon et al., 2000). However, the preliminary study has shown that plasma concentrations of cytokines may normalize during recovery from an acute episode of a major depressive disorder even without antidepressant treatment (Dahl et al., 2016). Interestingly, the proinflammatory cytokines and other factors secreted by peripheral Mφs, after crossing the blood-brain barrier, can activate local inflammation in the central nervous system (CNS) (Capuron and Miller, 2011; Moon et al., 2011). Subsequent activation of microglia may then result in the alteration of the synthesis and metabolism of neurotransmitters, including the increase of monoamine re-uptake (Leonard, 2010) or the inhibition of serotonin synthesis, as shown in depressed patients (Haroon et al., 2012). Besides, the depression-associated alterations of serotonin turnover can in turn dysregulate immune reactivity, as shown in the case of the T cells from depressed patients (González et al., 2007). Additionally, the CNS is widely colonized with resident Mφ populations consisting, apart from microglia, of choroid, meningeal and perivascular cells (Prinz et al., 2011) that play important immune and neuro-supporting functions (Roman et al., 2013) and may possibly be affected by depression-associated inflammation. Remarkably, polymorphisms in inflammation-related genes were reported to be associated with patient susceptibility to the development of major depression and antidepressant response as well (Wong et al., 2008). Altogether, these observations led to the first hypothesis regarding the inflammatory basis of depression (Hickie and Lloyd, 1995), now clarified as the "macrophage theory of depression" (Smith, 1991). Since these observations have significant translational potential, our review aims to briefly summarize the current data on the impact of the most commonly used antidepressant drugs on the immune response with special emphasis on the functions of Mφs.

2. Macrophage theory of depression

The observation that the symptoms of a major depressive episode could be a result of the administration of monokines to healthy volunteers became the first basis for the development of a "macrophage theory of depression" (Smith, 1991). It was further supported by the demonstration of the higher incidence of depressive symptoms in women and patients suffering from diseases associated with Mφ activation, like rheumatoid arthritis, coronary heart disease or stroke (Smith, 1991). Conversely, altered inflammatory response associated with depression is suspected to increase the risk of cardiovascular disorders (Dinan, 2009) and cancer development (Reiche et al., 2004). Additional evidence for Mφ involvement in the pathogenesis of depression results from observations that the use of cytokine inhibitors for the treatment of co-existing inflammatory disease in depressed patients also alleviated the symptoms of depression (Kulmatycki and Jamali, 2006), possibly by amelioration of the response to conventional antidepressant drugs (Miller et al., 2009). Accordingly, the therapeutic use of an infliximab, a TNFα antagonist, in a clinical trial, involving patients with depression resistant to conventional treatment, gave promising results (Raison et al., 2013). On the other hand, the most commonly used antidepressant drugs are suggested to possess additional anti-inflammatory activity (Eyre et al., 2016).

3. Anti-inflammatory activity of antidepressant drugs

The groups of drugs included into the pharmacotherapy of depression differ greatly in their pharmacological and chemical properties (Haenisch and Bönisch, 2011). However, from the current clinical point of view, the most relevant are drugs ameliorating the impaired process of neurotransmission. Those are represented by tricyclic antidepressant drugs (TCA), selective serotonin re-uptake inhibitors (SSRI), serotonin-norepinephrine re-uptake inhibitors (SNRI), and reversible monoamine oxidase (MAO)-A inhibitors. Interestingly, Mφs and other immune cells, due to the expression of serotonin (Shajib and Khan, 2015) and norepinephrine (Slota et al., 2015) receptors, can sense both, the depression-associated alteration of neurotransmitters' concentration and relations, and the clinically effective increase of the level of neurotransmitters in CNS synapses under the action of antidepressants.

Although one of the first human trials failed to find any changes in monocyte activity after co-treatment with moclobemide and dexamethasone (Landmann et al., 1997), antidepressant drugs were frequently shown to impact the dysregulated immune response in depressed patients (Lee and Kim, 2006), mostly by improving the serum cytokine profile during therapy (Hannestad et al., 2011; Janssen et al., 2010; Kenis and Maes, 2002), which may result from their influence on cytokine release (Kubera et al., 2001). Additionally, supplementation of cultures of peripheral blood mononuclear cells from healthy volunteers with imipramine modulated the secretion of cytokines, generally observed as inhibition of proinflammatory and enhancement of anti-inflammatory cytokines' release (Szuster-Ciesielska et al., 2003). Altogether, these observations suggest the anti-inflammatory and immunosuppressive potential of antidepressants.

At first, due to the impact of antidepressants on serotonin turnover, it can be speculated that antidepressants may alter the immune response at the early stage of cell recruitment to the site of inflammation, which among others depends on platelet-derived serotonin. Indeed, it was recently observed in a mouse experimental peritonitis that, while acute fluoxetine administration supported in vivo leukocyte interactions with endothelial cells by enhancing plasma serotonin concentrations, chronic treatment with fluoxetine impaired leukocyte rolling and adhesion on the endothelium (Herr et al., 2014). This suggests that the