Immunoregulatory natural compounds in stress-induced depression: An alternative or an adjunct to conventional antidepressant therapy?

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\textbf{ABSTRACT}

The interplay of chronic stress, neuroinflammation and altered immune reactivity has been shown to be important for the pathophysiology of brain disorders such as schizophrenia, depressive disorders and post-traumatic stress disorder. This immunoinflammatory theory has been extensively studied in the past three decades leading to the formation of the integrative discipline of psychoneuroimmunology. Targeting of the central nervous system by conventional pharmacotherapeutic methods is mainly through modulation of neuroendocrine systems such as the dopaminergic, GABA-ergic, adrenergic and serotoninergic systems. In recent years an increasing number of both experimental and clinical studies have shown that antidepressants can affect the immune system by reducing the production of pro-inflammatory cytokines such as IL-1\textbeta, IL-6 and TNF-\alpha. However, due to the serious adverse effects accompanying the chronic administration of psychoactive drugs there is a continuous need to produce novel therapeutics that are both potent and safe. The present review aims to summarize the current knowledge in the field of psychoneuroimmunology and to delineate the main interactions between stress, inflammation, immunity and the brain. Additionally, this paper explores the use of plant-derived molecules that display a strong anti-stress effect and simultaneously modulate the immune response as an alternative or adjuvant to classical antidepressant drugs.

\textbf{1. Introduction}

Stress accompanies human daily life in various forms and is generally defined as a state that disrupts homeostasis. Adaptation to stressful events depends on the duration and the intensity of the stressor. During acute stress, many physiological systems are activated that allow the body to survive. Acute stress prepares not only the cardiovascular, musculoskeletal and neuro-endocrine system for the “fight, flight or freeze” response under certain conditions, but also the immune system for eventual stress-induced challenges \cite{Dhabhar, 2018}. Immune cells express surface receptors for neurotransmitters generated in response to stress such as glucocorticoids and catecholamines. Clinical studies in people experiencing acute stress show its bidirectional effects on immune response which could result either in enhanced or suppressed immune function \cite{Cohen, 2006; Dhabhar, 2018}.

On the other hand, when the stress persists over long periods it leads to numerous, long-term adverse health effects \cite{Dhabhar, 2014, 2018}. Environmental factors as well as internal or external stimuli...
continuously disrupt the homeostasis. A life-threatening situation such as major physical trauma or prolonged fasting can significantly alter homeostasis and the body’s attempt to restore it often takes a lot of energy and natural resources that can lead either to a new level of homeostatic state (allostasis) or be interpreted itself as stress. Chronic stress factors can eventually lead to impairments and possible dysfunctions as the ability to maintain physiological functions are impeded. Many of these stress-induced disturbances weaken the protective function of the immune system by influencing humoral and cellular factors (Dhabhar, 2014; Dhabhar et al., 2012; Padro and Sanders, 2014). Clarification of the psychological and biological mechanisms by which chronic stress weakens an organism or exacerbates chronic disease would allow the development of behavioral and pharmacological treatment strategies aimed at alleviating or eliminating the harmful effects of stress (Chrousus and Kino, 2007; Jeon and Kim, 2017; Irwin and Cole, 2011).

Psycho-emotional distress, psychosomatic disorder, mental traumas, conflicts and extreme prolonged labor in stressful conditions affect the psycho-emotional status of an individual. This can lead to symptoms that affect mood (depression, tiredness and energy loss), concentration and behavior (Lupien et al., 2018). Chronic stress often co-occurs with a chronic inflammatory state represented with increased generation of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), disturbed tryptophan metabolism and decreased sensitivity of the glucocorticoid receptors (Dhabhar, 2018; Jeon and Kim, 2017; Maes, 2011). For instance, people suffering from major depressive disorder (MDD) are found to have elevated IL-6 levels (Hodes et al., 2016).

Considerable research in the last decade has been concentrated on the immuno-inflammatory mechanisms as a mode of treatment for psychiatric disorders. The term psychoneuroimmunology (PNI), i.e. immunopsychiatry refers to the interdisciplinary field that studies the heterogeneous interactions between the psycho-emotional processes, the neuroendocrine system and the immune response in the human organism (Cohen, 2006; Kim and Won, 2017; Pariante, 2015, 2017). Even though there is contention as to whether immune-mediated neuroinflammation is cause or a consequence within the complex clinical picture of stress-induced brain disorders, potent and safe anti-inflammatory agents that can cross the blood-brain barrier (BBB) are nonetheless needed. For example, many antidepressants are proven to have anti-inflammatory effects (Kenis and Maes, 2002). However, due to the significant adverse reactions to conventional psychoactive drugs there is a need for a novel therapeutic approach. Natural plant products are offering potent alternatives to classical antidepressants. Though the amount of experimental data on the effect of herbal extracts or pure plant-derived molecules that counteract the consequences of chronic stress is growing, to date no review specifically explores the effect of phytotherapeutics on immune-inflammatory response in brain disorders. This paper aims to review the current knowledge in the field of immunopsychiatry regarding the interconnections between chronic stress, immune response and neuroinflammation. In addition, the present review attempts to analyze experimental and clinical data concerning herbal substances that act on immune systems as both anti-stress and anti-inflammatory agents.

2. Chronic stress and brain disorders

The most common psychopathologies associated with chronic stress and immuno-inflammation are depressive disorders, post-traumatic stress disorder (PTSD) and schizophrenia (Lupien et al., 2018; McEwen, 2000).

Depressive disorders are strongly correlated with acute and chronic stress (Pizzagalli, 2014; Slavich and Irwin, 2014). Increased levels of pro-inflammatory cytokines in patients with major depressive disorder could induce neurotoxicity resulting in both functional and structural brain alternations which is comprehensively reviewed by Kim and Won (2017). Inflammation and elevated immune response found in a large portion of depressive phenotypes permits the definition of a specific subtype of depressive disorder: inflammation-induced depression (Jeon and Kim, 2017; Maes, 2011; Miller and Raison, 2015).

Patients with PTSD have suppressed reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which results in elevated catecholamines and corticotropin-releasing hormone (CRH), but low circulating cortisol (Lupien et al., 2018). In addition, PTSD leads to deregulated immune response represented by elevated pro-inflammatory cytokines such as IL-6, TNF-α and IL-17 and decreased IL-4 (Wang et al., 2016).

3. Neuroinflammation and cytokines involved in stress response

Under stress, the sympathetic nervous system (SNS) is the first to be activated. This induces a rapid stress response with increased release of noradrenaline and adrenaline followed by physiological reactions such as elevated pulse and increased metabolic rate. Subsequently, as part of the delayed stress response, the activation of the HPA axis provokes the hypothalamus to secrete CRH and antidiuretic hormone (ADH) and the pituitary - adrenocorticotropic hormone (ACTH) into the systemic circulation. Approximately 10 min after the action of a stress factor, glucocorticoids are released from the adrenal gland and, 30 min later, glucocorticoid secretion reaches its peak and then decreases (Ulrich-Lai and Herman, 2009).

Apart from these main neuroendocrine mediators, there are many other parameters of the complex network involved in the body’s resistance to stress. The immune cells which are circulating in the blood stream, but also distributed to certain degree in every tissue, have receptors to many neuroendocrine mediators such as ACTH, glucocorticoids, catecholamines, endogenous opiates, prolactin, melatonin, testosteron, estrogen, etc. (Besedovsky and Rey, 2007). The immune system is thus directly influenced by the varying concentrations of these neuroendocrine mediators (Glaser and Kiecolt-Glaser, 2005). Conversely, the immune cells could affect the neuroendocrine system via secretion of cytokines. Although the BBB excludes water-soluble substances, circulating peptides and proteins from the brain, this barrier is missing in the thermoregulatory region, i.e. the hypothalamic fronto-optic core, which allows the penetration of cytokines from the blood into the brain. Neurons express receptors for pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 that could induce activation of the HPA axis and affect the nervous system (Wohleb et al., 2013).

Neuroinflammation or elevated microglial activity is correlated with several mental illnesses. In response to stressful stimuli, the microglia experience changes either as a result of increased number due to proliferation or via enrolment of monocytes from the peripheral blood. This leads to an inflammatory glial response represented as production of pro-inflammatory cytokines and expression of several cell surface antigens (Frick et al., 2013; Walker et al., 2014; Wohleb et al., 2013). The interaction between the nervous, the endocrine and the immune-inflammatory systems induced by stress is summarized in Fig. 1.

Stress exposure activates the hypothalamic-pituitary-adrenal (HPA) axis, which initiate production of corticotropin-releasing hormone (CRH) from hypothalamus to the pituitary gland. Adrenocorticotropic hormone (ACTH) secreted from the pituitary activates the adrenal glands which results in stress-induced release of glucocorticoids (GC), noradrenaline (NA) and adrenaline (A). The pituitary also produces growth hormone (GH) and prolactin. All these hormones are sensed by the immune cells. Simultaneously with the HPA axis the autonomic nervous system responds to stress resulting in activation of the sympathetic nervous system’s innervation (SNS) and the parasympathetic nervous system’s innervation (PSNI). Both SNS and PSNI produce an effect on the lymph nodes and increase immune cell trafficking to the peripheral blood. Finally, the activated immune cells produce various cytokines in response to stress, many of which could cross the blood-brain barrier (BBB) and activate the resident immune cells, i.e.
microglia, to also produce cytokines and provoke neuroinflammation in the brain.

The brain lacks a lymphatic system and neurons do not normally express the human leukocyte antigen class II (HLA-II) molecules required for antigen-specific immune response activation. However, it is possible to activate an immune response in the CNS under certain circumstances. Bone marrow-derived cells such as perivascular macrophages and microglia that express the HLA-II and can present antigens are part of the CNS; additionally, astrocytes and endothelial cells could play a role of antigen presenting cells (APCs) and are able to release pro-inflammatory cytokines when activated. The microglial cells synthesize and respond to cytokines such as IL-1β, IL-6, TNF-α, tumor necrosis factor beta (TNF-β), interferon gamma (IFN-γ), transforming growth factor beta (TGF-β) as well as colony stimulating factors (CSFs).

The IL-1β induces astrocyte proliferation and subsequent release of other cytokines from the astrocytes. The TNF-α and TNF-β are capable of damaging the oligodendrocytes, a source of myelin in the brain. In addition, activated peripheral T-lymphocytes may penetrate the BBB and release cytokines that increase HLA-II expression in surrounding endothelial cells, further increasing the permeability of the BBB and accelerating the rate at which B-lymphocytes can penetrate into the brain (Frick et al., 2013; Walker et al., 2014). This evidence suggests that the immune system is capable of causing neuroendocrine responses and gives reason to assert that it is a peripheral receptor organ that transmits brain information about endogenous or exogenous stress stimuli (Beedovsky and Rey, 2007).

4. Psychoactive drugs and their effect on immune response in stress-induced disorders

In recent years, an increasing number of psychopharmacological studies exploited the immune-inflammatory theory of stress-induced disorders to evaluate the effect of psychoactive drugs on the immune system (Felger and Lotrich, 2013; Hiles et al., 2012). The clinical efficacy of antidepressants is related to their immunomodulatory properties (Rensis and Maes, 2002). For example, the decrease in TNF-α levels during therapy is associated with a good antidepressant response, whereas the IL-6 elevation is associated with an unsatisfactory one (Lichtblau et al., 2013).

Antidepressants, as a first-line therapy for stress-induced disorders and depressive disorders, continue to be a subject of intense study, particularly relating to their immunomodulatory effects. Apart from their main mechanism of action – the inhibition of the reuptake of certain neurotransmitters - antidepressants also produce significant reduction in pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, IL-17 (Gobin et al., 2014; Hiles et al., 2012).

Considering the immunomodulatory effects of the selective serotonin reuptake inhibitors (SSRIs), special attention is paid to the role of serotonin (5HT) signaling on immune cells (Gobin et al., 2014). Not only do SSRIs have the ability to affect healthy lymphocytes, but they also influence the viability of some immune cancer cells. Given that serotonin is involved in T-cells activation, the authors propose that the anti-proliferative action of fluoxetine may be due to inhibition of 5-HT uptake in T-lymphocytes (Amit et al., 2009). Another possible mechanism for the effect on T-cells by SSRIs is suggested by Gobin et al. (2015), as they found that fluoxetine suppresses the intracellular calcium signaling.

In an in vitro experiment, Munzer et al. (2013) investigated the effects of citalopram, mirtazapine and escitalopram on the secretion of a panel of cytokines in activated T and B-lymphocytes. Their study found that citalopram increased the levels of IL-1β, IL-6, IL-22 and TNF-α, while escitalopram reduced the IL-17 levels. As a probable cause of the observed differences in the effect of the two SSRIs on the cytokines profile, the researchers pointed out the different stereochemical
### 5. Plant extracts and their bioactive molecules with effect on immune-inflammatory response in stress-induced disorders

Natural products and, more specifically, medicinal plant species have been utilized for centuries in the treatment and management of various pathological conditions (Georgiev, 2014). Stress-induced disorders are characterized by changes in the CNS that involve a plethora of neuronal pathways, suggesting that the therapy against such multifactorial conditions should target more than one neuroendocrine system. Plant extracts comprise complex mixtures of usually more than one bioactive molecule and so the conventional pharmacological concept of “one drug – one receptor – one disease” is not easily applicable to explain their mode of action. In general, phytotherapeutics that are known to act on the CNS are classified into several categories according to their main action in the brain: antidepressant, sedative, nootropic, and adaptogenic.

Ethnopharmacologically among the most extensively studied plants for their psychotropic action are Hypericum perforatum L., Valeriana officinalis L., Passiflora incarnata L., Crocus sativus L., Curcuma longa L., Rhodiola rosea L., Coffea arabica L., and Cannabis sativa L. (Panossian et al., 2018; Sarris et al., 2011; Shafiee et al., 2017).

Plant extracts that non-specifically increase an organism’s resistance to stress are characterized by changes in the CNS that involve a plethora of neuronal pathways, suggesting that the therapy against such multifactorial conditions should target more than one neuroendocrine system. Plant extracts comprise complex mixtures of usually more than one bioactive molecule and so the conventional pharmacological concept of “one drug – one receptor – one disease” is not easily applicable to explain their mode of action. In general, phytotherapeutics that are known to act on the CNS are classified into several categories according to their main action in the brain: antidepressant, sedative, nootropic, and adaptogenic.

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to stress via modulation of the two main stress control systems in the body namely the HPA axis and the SNS, are termed adaptogens (Panossian et al., 2009). Studies on their mechanism of action have shown enhancement of the production of neuroactive Y (NPY) and heat-shock protein 72 (Hsp72), which promotes relaxation and increases neuronal plasticity and adaptability (Panossian and Wikman, 2010; Panossian et al., 2012).

Plant adaptogens alleviate the negative effects on health from prolonged exposure to stress, and this is at least in part a result of immunomodulation. Our previous studies found that treatment of stressed rats with extracts from *Rhodiola rosea* L. and *Curcuma longa* L. as well as their respective marker substances, salidroside and curcumin, attenuate the production of both IL-6 and TNF-α levels in brain tissue and in serum (Vasileva et al., 2017, 2018). Salidroside has been previously reported to inhibit the pro-inflammatory cytokines’ production in depression models (Yang et al., 2014; Zhu et al., 2015).

Special attention has been generated by the antidepressant potential of curcumin – the active compound of *Curcuma longa* L. – which is a strong natural antioxidant with potent inhibiting activity against pro-inflammatory factors. For this reason, it has been implemented within the therapy for osteoarthritis, inflammatory bowel disease, certain types of cancer (e.g. colorectal carcinoma) and other diseases (Salehi et al., 2019). In recent years, extensive studies revealed the profound activity of curcumin on depressive and stress-induced disorders, especially regarding the accompanying immune-inflammatory dysregulations, both in experimental and clinical settings (Jiang et al., 2013; Kaufmann et al., 2016; Lopresti et al., 2014; Vasileva et al., 2018). However, despite the diverse range of beneficial activities designated to this natural compound there are also some controversies about its mechanisms of action. One is the extensively discussed bioavailability of curcumin (Aggarwal et al., 2013). Another recently reported problem is that it could give interference in some biological screening assays leading to false-positive results (Baell and Nissink, 2018).

Zhang et al. (2017b) aimed to examine the antidepressant-like effect of sulforaphane a potent natural antioxidant and nuclear factor erythroid 2-related factor 2 (Nrf2) activator derived from plants of the Brassicaceae family. Interestingly, the authors reported that pretreatment with sulforaphane (30 mg/kg bw, p.o.) resulted in a strong reduction of the immobilization time on forced swim test and a decrease of the production of the pro-inflammatory cytokine TNF-α but had no effect on the levels of the anti-inflammatory IL-10 (Zhang et al., 2017b).

In similar experimental set-up, Jiang et al. (2017) provided evidences that proanthocyanidins (80 mg/kg bw, p.o.) from *Vitis vinifera* L. dose-dependently decreased the LPS-induced neuroinflammation via inhibition of the NF-κB pathway in the hippocampus of depressed mice. The authors reported decreased levels of IL-1β, IL-6 and TNF-α in brain tissue as a result of the proanthocyanidin administration (Jiang et al., 2017). Further, Liu et al. (2014) reported that treatment with extract from *Hemerocallis citrina* (130 mg/kg bw, p.o.) produces an antidepressant-like effect in chronically stressed rats and suggested that this effect could be mediated through inhibition of neuroinflammation represented by decreased levels of IL-1β, IL-6 and TNF-α in the prefrontal cortex (PFC) in rats (Liu et al., 2014).

Natural compounds such as bilobalide, ginsenoside, rosmarinic acid, salvianolic acid and hesperidin are exploited for their strong anti-inflammatory effects in studies of different models of brain illnesses (Sui et al., 2019; Yu et al., 2019). Some of the plant-derived natural substances that have gained focus for their effect on cytokines and neuroinflammation in experimental models of stress and depression are shown in Table 2. Promising behavioral outcomes, along with attenuation of inflammatory mediators, are shown for the herbal molecules in these studies. In some cases, the decrease in the stress-induced production of TNF-α, IL-1β and IL-6 in brain tissue was comparable to that of a positive control, indicative of possible common modes of action between the studied phytochemicals and conventional antidepressants such as fluoxetine (Cheng et al., 2018; Vasileva et al., 2017;
known to impair normal cells along with eliminating cancer cells. Seo et al. (2018) found that addition of plant extracts to a fixed combination of cytostatics alleviated the negative effects from the chemotherapy on neuroglial cells. Further detailed studies are required to confirm and develop the idea of effective hybrid combinations between synthetic drugs and natural compounds (Wagner and Effert, 2017). Hypothetically such hybrid combinations could be tested in the therapy of various medicinal conditions as well as in stress-induced disorders. The use of conventional antidepressants is usually prolonged and accompanied with serious systemic adverse effects including weight gain, sexual dysfunctions, sleep disturbances, addiction, withdrawal syndrome and suicidal ideations. Investigation into combinations of synthetic antidepressants and plant molecules with promising anti-stress and anti-inflammatory effects could result in viable hybrid combinations with improved efficacy and/or safety in the chronic therapy of depressive disorders. Moreover, such studies should implement “omics” techniques such as metabolomics, pharmacogenomics and proteomics to clarify the detailed mechanism of interaction between the components included (Chen et al., 2018; Sahoo and Brijesh, 2019).

6. Conclusions

In the past three decades, the field of psychoneuroimmunology has witnessed tremendous progress. The role of chronic stress and immune-inflammation as risk factors for brain disorders such as MDD or PTSD is unquestioned. Understanding the cytokine profiles of stress-induced psychopathologies would aid not only the early diagnosis of stress-induced brain disorders but will eventually be of great importance in both the choice of proper therapy and the development of novel treatments. Many experimental and clinical studies have confirmed that the antidepressant effect of the SSRIs is mediated partly via immunomodulation. Plant-derived molecules with antidepressant-like effect are of great scientific interest as many of these phytotherapeutics show properties comparable to that of conventional antidepressants. Furthermore, natural compounds with significant anti-inflammatory effects warrant further investigation regarding their use in hybrid combinations with synthetic psychoactive drugs.

Conflicts of interest

The authors declare that the present work is not a subject of any potential conflict of interest.

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Appendix A. Supplementary data

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Fig. 2. Chemical structures of selected natural compounds with potential antidepressant-like effects.
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