Pharmacological Reports
2013, 65, 1663–1672
ISSN 1734-1140

Review

Macrophages and depression – A misalliance or well-arranged marriage?

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Abstract:
Depression is a severe medical condition with multiple manifestations and diverse, largely unknown etiologies. The immune system, particularly macrophages, plays an important role in the pathology of the illness. Macrophages represent a heterogeneous population of immune cells that is dispersed throughout the body. The central nervous system is populated by several types of macrophages, including microglia, perivascular cells, meningeal and choroid plexus macrophages and pericytes. These cells occupy different brain compartments and have various functions. Under basal conditions, brain macrophages support the proper function of neural cells, organize and preserve the neuronal network and maintain homeostasis. As cells of the innate immune system, they recognize and react to any disturbances in homeostasis, eliminating pathogens or damaged cells, terminating inflammation and proceeding to initiate tissue reconstruction. Disturbances in these processes result in diverse pathologies. In particular, tissue stress or malfunction, both in the brain and in the periphery, produce sustained inflammatory states, which may cause depression. Excessive release of pro-inflammatory mediators is responsible for alterations of neurotransmitter systems and the occurrence of depressive symptoms. Almost all antidepressive drugs target monoamine or serotonin neurotransmission and also have anti-inflammatory or immunosuppressive properties. In addition, non-pharmacological treatments, such as electroconvulsive shock, can also exert anti-inflammatory effects. Recent studies have shown that antidepressive therapies can affect the functional properties of peripheral and brain macrophages and skew them toward the anti-inflammatory M2 phenotype. Because macrophages can affect outcome of inflammatory diseases, alleviate sickness behavior and improve cognitive function, it is possible that the effects of antidepressive treatments may be, at least in part, mediated by changes in macrophage activity.

Key words:
macrophages, microglia, cytokines, depression, antidepressants, electroconvulsive shock (ECS)

Abbreviations: BDNF – brain-derived neurotrophic factor, BH4 – tetrahydrobiopterin, CNS – central nervous system, CRH – corticotropin-releasing hormone, ECS – electroconvulsive shock, GR – glucocorticoid receptor, HPA – hypothalamus-pituitary-adrenal, IDO – indoleamine 2,3-dioxygenase, IFN – interferon, IL – interleukin, MHC – major histocompatibility complex, NMDA – N-methyl-D-aspartate, NO – nitric oxide, RNS – reactive nitrogen species, ROS – reactive oxygen species, TNF-α – tumor necrosis factor α

Introduction

Depression is a severe, heterogeneous syndrome, and it is one of the major contributors to the global burden of all diseases [33]. Its relatively low heritability indicates the importance of environmental factors as a cause of depressive episodes, particularly exposure

to stressful life events and immunological challenges. The variability of symptoms and disease course as well as the varied response to a wide range of treatments suggest diverse etiologies and pathomechanisms of the disease. Noradrenergic and serotonergic neurotransmission deficiencies have been recognized to play the main role in the pathology of depression [41]. Nevertheless, other neurotransmitter systems [47] and immuno-endocrine mechanisms appear to be involved [4].

Immunological abnormalities in the course of depression have been reported since the 1970s. An increasing body of evidence in this field has resulted in elucidating the macrophage theory of depression [51], as the excessive activity of macrophages and their products, i.e., pro-inflammatory cytokines, has been noted as an important factor in the etiopathology of this illness. Further studies substantially broadened the potential range of the psycho-neuro-immune interactions, integrating the effects of stress, neuroanatomical changes and aberrations in the immune system into the immune theory of psychiatric diseases [4]. Similar to the original concept [51], the latest studies have emphasized the roles of different types of macrophages in the pathophysiology of depression.

Depressive symptoms frequently accompany systemic inflammatory diseases. Furthermore, depressive behavior can be induced by immune factors, and effective antidepressive treatment typically normalizes indices of inflammation. These findings imply that macrophages and the immune system as a whole may be regarded as potential targets of antidepressive treatments.

Macrophages

Macrophages are cells of the immune system that originate from the myeloid cell lineage [59]. They are present in all tissues and show substantial morphological and phenotypic heterogeneity and have diverse physiological functions. In mammals, all macrophages derive from the yolk sac, fetal liver and bone marrow. Myeloid progenitors derived from the yolk sac colonize all tissues during fetal life and develop into resident tissue macrophages, including Langerhans cells (skin), Kupffer cells (liver) and microglia (central nervous system; CNS). After birth, the bone marrow constitutes the main source of myeloid cells, which differentiate into circulating monocytes and their progeny, dendritic cells and macrophages.

Resident tissue macrophages, including brain microglia, are not replaced by bone marrow progeny. They participate in proper tissue development and homeostasis. After injury or pathogen invasion, they recognize danger signals, change their morphology and start to secrete cytokines and other immunomodulators, which attract circulating immune cells and coordinate the immune response [34].

Under inflammatory conditions, circulating monocytes migrate into target sites and differentiate into inflammatory dendritic cells and macrophages [12]. They mediate pathogen and damaged cell clearance, trigger specific immune responses and, lastly, terminate inflammatory processes, allowing tissue remodeling and repair. Depending on local or systemic stimuli, e.g., the presence of specific cytokines, macrophages perform different tasks and can stimulate or inhibit various aspects of tissue metabolism. Moreover, the same cells can repeatedly change their functional phenotype and adjust their activity to current demands determined by the local microenvironment [5]. When stimulatory factors disappear, macrophages return to their basal, resting state, and such functional plasticity is unique among all the cells of the immune system.

Monocyte-derived macrophages can be divided into two functionally distinct subpopulations named M1 and M2 due to their association with the respective types of immune response, Th1 and Th2 [5]. Such functional dichotomy is reflected by different sets of surface markers and released cytokines and their roles in the immune response. M1, or classically activated, macrophages are characterized by high expression of major histocompatibility complex (MHC) class II antigen, pro-inflammatory cytokine (e.g., IL-1β, IL-12, TNF-α) release and intense synthesis of reactive nitrogen and oxygen species (RNS and ROS, respectively), and they are engaged in inflammatory, microbicidal and tumoricidal processes. M2, or alternatively activated, macrophages display high phagocytic activity, anti-inflammatory and regulatory cytokine (e.g., IL-4, IL-10, IL-13) release, high arginase activity and high expression of numerous endocytic receptors (e.g., scavenger receptors, hemoglobin and mannose receptors). They participate in antibody synthesis, parasite clearance, termination of inflammation, tumor progression, tissue remodeling and immunoregulation.

The aforementioned subpopulations of macrophages represent two poles of qualitative macrophage activity. However, depending on microenvironmental cues, a continuum of macrophage activation states exists both in terms of quality (from the M1 to M2 type) as well as intensity (from quiescent to fully activated, regardless of the direction) [32, 50]. Excessive, uncontrolled activation of one of the types of macrophages or aberration of the functional phenotype switching results in different pathologies, e.g., atherosclerosis (M1) or asthma (M2).

Regarding the degree of activation, under homeostatic conditions, macrophages are in a basal, resting state, and they perform their normal, physiological functions. Infection, tissue malfunction or damage is sensed in the first instance by macrophages. They undergo activation to a level adequate to counter the intensity of noxious stimuli. However, infection and tissue damage are strong and dangerous stimuli and, in most cases, the result in full-spectrum inflammatory activation. Tissue stress and malfunction are low-grade noxious stimuli and also induce low-grade activation, intermediate between the homeostatic and inflammatory states [32]. These processes, called para-inflammation, are adaptive responses to a changed environment. However, when continued for a long time, para-inflammation may result in a wide range of pathological conditions, including among others, depressive disorders [15, 32].

Macrophages in the brain

Several types of macrophages reside in the brain, including microglia, perivascular cells, meningeal and choroid plexus macrophages and, in some respects, pericytes [40]. These subtypes originate from various precursors and occupy different compartments of the brain. They differ in terms of their morphology, physiological properties and function. As cells of the innate immune system, they act as the first line of defense against invaders, and they also sense and react to tissue malfunction or damage. However, their activity goes beyond a defensive role. In the steady state, brain macrophages maintain the proper function of neural cells as well as organize and preserve the neuronal network. Under pathological conditions, they may be deleterious to neurons and exacerbate tissue damage and the course of the disease.

Microglia

Microglia are cells of the myeloid lineage derived from precursors that colonize the developing brain during fetal life [59]. They express typical macrophage surface markers, such as Fc and complement receptors, CD11b and F4/80, but their exact phenotypic properties are related to the region of the brain and functional state of the cells. Depending on the brain structure, the density of microglial cells varies from 0.5 to 16.6% (in humans) and is generally greater in white matter than in gray matter.

In the adult brain under homeostatic conditions, microglial cells show ramified morphology, with fine, long processes penetrating the brain parenchyma [24]. Each cell occupies a rather fixed position, but their extensions are highly motile and continuously scan their territory for endogenous or exogenous danger cues. They constantly monitor the synaptic status during short-lasting contact of their extensions with synapses and proceed with their degradation or creation, thus remodeling synaptic circuits. With a wide range of surface receptors, microglia can also sense disturbances in the concentration of neurotransmitters and neuromodulators, indicating improper neuronal activity. Microglia are the main phagocytic cells inside the CNS that remove unnecessary or damaged cells, parts of cells and debris. They promote the neurogenesis and reorganization of neural tissue by secreting numerous trophic factors [24]. Similar to peripheral macrophages, microglia exhibit functional polarization, and this property plays an important role in maintaining brain homeostasis [34] as well as in ischemia, altered neuronal activity and any other loss of brain homeostasis resulting in a shift in the activation state of microglial cells [29]. They change their morphology to an amoeboid shape, release inflammatory and chemotactic factors and acquire the abilities to migrate, proliferate and perform phagocytosis. Depending on the nature of the activating signals and their context, microglial cells can express different reactive phenotypes, similar to peripheral macrophages. Moderate- and short-term disturbances result in the activation of microglia in the range necessary for the elimination of dysfunction without the engagement of an immune response or alterations of other systems of the body. In such situations, microglia play a protective role, and their activity is sufficient for the restoration of homeostasis [29]. In the presence of intense or long-lasting stimuli, microglia undergo strong activa-

tion and become neurotoxic. They release pro-inflammatory cytokines, chemotactic factors, ROS and RNS, which aggravate tissue damage and also recruit monocytes from the blood. These immigrant monocyte-derived macrophages take over the functions that are no longer supported by microglia due to their malfunction. In an optimal scenario, they eliminate the pathology, restrict local inflammatory processes and promote tissue renewal and neuroprotection. After the restoration of homeostasis, both local microglia and monocyte-derived macrophages become morphologically indistinguishable; however, they can maintain subtle changes that render them more sensitive to further stimuli [24, 29].

Perivascular macrophages

Perivascular cells, also named perivascular macrophages or perivascular microglia, are low in number within the population of bone marrow-derived cells occupying the space between the vascular basement membrane surrounding endothelial cells and pericytes and the glia limitans [58]. They have an elongated or amoeboid morphology with branching processes that enwrap the blood vessels on which they reside. Perivascular cells possess phagocytic capacity and express numerous surface markers typically found on peripheral macrophages. Although at a small rate, under basal conditions, they are continuously replaced by blood monocytes. After inflammatory stimulation, the turnover ratio substantially increases. These cells comprise a part of the blood-brain barrier and also play an important role in immune-to-brain communication, transmitting and modulating peripheral inflammatory signals to the brain [26, 58].

Meningeal macrophages and choroid plexus macrophages

Meningeal macrophages and choroid plexus macrophages are associated with the arachnoid and pial vasculature and choroid plexus stroma, respectively. They are located at the lines separating the blood from cerebrospinal fluid. Both populations of macrophages are monocyte derived and are similar to perivascular macrophages in their properties and functions [10, 31].

Pericytes

Pericytes are cells embedded within and completely covered by the basement membrane of blood vessels, including pre-capillary arterioles, capillaries and post-capillary venules, in close proximity to endothelial cells [1]. They are particularly frequent on microvessels of the brain where the pericyte to endothelial cell ratio is approximately 1 : 3 (for example, in striated muscle, this ratio is 1 : 100). Pericytes are irregular in shape and possess numerous branched processes that partially encircle the vessels. They originate from mesodermal precursors migrating into the tissues during vascularization. Similar to other macrophages, they express the CD11b surface marker, respond to interferon γ (IFN-γ) stimulation by the upregulation of MHC class II antigens and exhibit phagocytic and antigen-presenting potential. Together with endothelial cells, astrocytes and other perivascular cells, pericytes comprise the blood-brain barrier and play an important role in blood-to-brain communication [6]. They also constitute the first line of immunologic defense in the brain. The pericytes of capillaries are contractile and can regulate local blood flow. They are very sensitive to ROS and RNS and contract under hypoxic conditions. Lastly, they may function as pluripotent stem cells.

Macrophages in the pathology of depression

Depression is manifested by diverse symptoms, including abnormalities affecting mood, cognition, psychomotor activity and neuroendocrine, immune and vegetative functions. An increasing number of reports in the literature show that almost all of these disturbances may be related to the action of pro-inflammatory cytokines released by macrophages, both in peripheral locations as well as the brain [4, 27, 34, 51]. Moreover, inflammation appears to be one of the main processes contributing to diseases that frequently co-occur with depression, e.g., atherosclerosis, rheumatoid arthritis and obesity [52, 57].

Circulating monocytes and tissue macrophages represent a large population of immune cells dispersed throughout the body [59]. As cells of the innate immune system, they are the first to recognize

any disturbances in homeostasis and secrete a respective set of cytokines, thus orienting the immune processes in the body. The inflammatory response develops after the recognition of disturbances, and pro-inflammatory mediators are secreted at the beginning of the immune reaction. Peripherally generated pro-inflammatory signals are transmitted into the CNS and induce sickness behavior – a complex of behavioral manifestations resembling a depressive state. A great number of reports corroborate this notion. The first observation of the role of cytokines in disturbances of mental states was that patients therapeutically receiving the pro-inflammatory cytokine interferon-α (IFN-α) developed several depressive symptoms that faded when treatment with the cytokine was ceased [51]. Recent studies have demonstrated increased levels of pro-inflammatory cytokines, i.e., IL-6 and TNF-α (and IL-1β, but not in all studies), in the circulation of depressed patients. Increased levels of other inflammatory indices, e.g., C-reactive protein and neopterin, are also frequently reported [36].

However, inflammation-induced sickness behavior in laboratory animals does not strictly resemble the depressive episodes experienced by humans. Some of the features of depression, for example, sadness, guilt, suicidality and feelings of worthlessness, cannot be modeled in animals. However, pyrexia generally associated with sickness is not a symptom experienced by depression sufferers. Additionally, the cytokine levels observed in depressive patients are far lower than those observed in inflammatory states.

There are several pathways through which pro-inflammatory signals reach the brain [16, 27]. These include (i) active transport from the circulation to the brain through specific transporters, (ii) a leaky blood-brain barrier that occurs in depression or fenestrated areas of the blood-brain barrier such as the circumventricular organs and (iii) activation of endothelial cells and macrophages (perivascular and meningeal macrophages, pericytes) lining the cerebral vasculature, producing inflammatory mediators inside the brain and activating microglia. The stimulation of peripheral afferent nerve fibers (e.g., the vagus nerve), which transmit signals to relevant brain regions, is regarded separately. Lastly, immune cells may enter the brain from the blood and release pro-inflammatory mediators directly into the brain parenchyma [24, 29].

Cytokines, when reaching the CNS, exert profound effects on a wide range of neurobiological processes related to depressive behavior and depression-related somatic disturbances. Regardless of the specific mechanisms, macrophages play an important role in these processes due to their ability to recognize alterations and release pro-inflammatory mediators, which initiate the response of the CNS. The reaction to pro-inflammatory signals involves neurons and glial cells and includes disturbances in the synthesis and metabolism of neurotransmitters, alterations in neurogenesis and neural plasticity as well as neurotoxicity.

Pro-inflammatory cytokines and prostaglandins can induce microglia to produce indoleamine 2,3-dioxygenase (IDO), an enzyme that converts the serotonin precursor, tryptophan, to kynurenine. In addition, activation of the kynurenine pathway produces additional metabolites: 3-hydroxykynurenine (causing oxidative stress) and quinolinic acid, a strong agonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor. These compounds are potentially neurotoxic and, as a result, contribute to depression [16, 60]. Thus, increased IDO activity leads to serotonin depletion and, concurrently, to amplification of glutamatergic neurotransmission and an increase in oxidative stress; all of these processes are commonly observed in depression [35, 36].

Over-activity of the glutamatergic system is regarded as an important pathomechanism of depression [47]. This neurotransmitter mediates the vast majority of excitatory transmission in the brain and is engaged in cognition and emotion, processes that are commonly affected in depression. Glutamatergic abnormalities in the plasma, cerebrospinal fluid and brain of depressive patients have been reported. Functional *in vivo* measures show elevated glutamate levels in the various brain regions. The signs commonly observed in depression, such as reduced dendritic arborization and spine density, decreased numbers of neurons, oligodendrocytes and astrocytes and microglial activation, are related to excessive levels of glutamate and increased glutamatergic neurotransmission [2, 4]. Pro-inflammatory cytokines promote the synthesis of the endogenous glutamate receptor agonist quinolinic acid, increase glutamate release and inhibit glutamate re-uptake by astrocytes. Moreover, activation of NMDA receptors perpetuates the pro-inflammatory activity of microglia, thus participating in the pathology of depression [16, 47].

In addition to disturbances in serotonergic neurotransmission, pro-inflammatory cytokines can affect other neurotransmitter systems, including the adrener-

gic, noradrenergic and dopaminergic systems, as well as the neuromodulator, nitric oxide (NO) [54]. Such action is mediated by alteration of the synthesis of tetrahydrobiopterin (BH4), which is a co-factor of several enzymes involved in the metabolism of the following amino acids, which are precursors of the aforementioned neurotransmitters: phenylalanine, tyrosine and tryptophan. BH4 is also a co-factor of NO synthases. NO plays multiple roles as a neuromodulator, which can interfere with dopaminergic, serotonergic and cholinergic neurotransmission, and as a cytotoxic molecule of activated macrophages, monocytes and granulocytes in the innate immune response. Increased synthesis of NO is related to depressive states, and decreasing NO synthase activity may be beneficial [9]. However, in cases of an insufficient BH4 supply, NO synthases produce superoxide anion, which reacts with residual NO and may generate oxidative stress, leading to neurotoxicity [54].

Pro-inflammatory cytokines have been shown to increase monoamine and serotonin re-uptake, thereby reducing their availability in the synaptic cleft and decreasing neurotransmission [27]. All of these processes result in decreased monoaminergic and serotonergic neurotransmission and increased glutamatergic tone, which are considered to play the primary roles in the pathology of depression [41, 47].

However, acute monoamine or serotonin depletion results in mood disturbances only in predisposed persons with a family history of depressive illness or in remitted patients, not in healthy individuals [46]. This suggests that monoamine and serotonin deficiencies are not the sole causes of depression pathology and implies that other mechanisms are involved.

In addition to the alterations of neurotransmitter systems, pro-inflammatory cytokines contribute to depressive symptoms by activating the hypothalamus-pituitary-adrenal (HPA) axis and inducing glucocorticoid resistance and hypercortisolemia, features commonly observed in depressive states [16]. It has been proposed that inflammatory activation of the immune system is perceived and processed by the brain as a stressor and results in corticotropin-releasing hormone (CRH) release from the hypothalamus and subsequent activation of the HPA axis. Increased glucocorticoid levels, in turn, inhibit HPA axis activity. However, pro-inflammatory mediators can decrease glucocorticoid receptor (GR) expression and alter GR functions, thus resulting in glucocorticoid resistance in both the CNS and the periphery [39].

Pro-inflammatory cytokines influence the function of the CNS through neurogenesis, alterations in neural circuits and neurodegeneration. Under physiological conditions, pro-inflammatory cytokines play a positive role by providing trophic support for neurons, but their overproduction in inflammatory states has deleterious effects. Neurogenesis in the adult brain is a recently discovered phenomenon, and it is thought to be involved in many processes, including learning and memory, which are commonly impaired cognitive functions in depression [25]. Pro-inflammatory mediators may affect these functions by decreasing the expression of trophic and growth factors, e.g., brain-derived neurotrophic factor (BDNF). Insufficient support by these molecules may impair not only cell proliferation and survival but also affect the integration of new neurons into neural networks. Taken together, these processes may result in changes in the brain structure and synaptic plasticity and lead to neurodegeneration, as revealed by cellular loss and the decreased volume of several brain areas related to depression [2, 18].

In addition to immunological factors, stress is regarded as another major causative factor of depressive states [28]. Stress can promote inflammatory responses in the periphery through the sympathetic nervous system. Glucocorticoids increase the release and decrease the clearance of glutamate, perpetuating glutamate toxicity as well as decreasing the synthesis of trophic factors [2]. In the brain, microglial cells form direct connections with synapses, and stress directly activates microglia through neural stimuli to release pro-inflammatory mediators, i.e., cytokines and prostaglandins [16]. Thus, in relation to depressive illness, many of the effects of stress may be the result of their pro-inflammatory action.

The abovementioned roles of various types of macrophages in the pathomechanisms of depression presume the existence of peripheral or central chronic, non-resolving inflammatory processes that may be causative of depressive states. There are several such situations.

One of these situations may be the presence of chronic inflammatory diseases such as atherosclerosis, rheumatoid arthritis or obesity [52, 57]. Recently, in a model of chronic colitis, an inflammatory disease co-occurring with depression, Ghia et al. [13] demonstrated the important role of macrophages in the relationship between depression and peripheral inflammation. Using this mouse model, they demonstrated that induction of a depressive state reactivated quies-

cent inflammatory colitis, and macrophages isolated from depressed mice expressed a pro-inflammatory functional phenotype [13]. They also demonstrated that the transfer of macrophages from mice with depression-like behavior exacerbated the inflammatory disease course [14].

A so-called leaky gut may be another chronic inflammatory stimulus. Commensal microbiota in the digestive tract can drive regulatory mechanisms and maintain the pro- and anti-inflammatory balance in the immune system. In sera from depressed patients, Maes [30] reported an increased level of antibodies to LPS derived from several gut bacteria together with increased inflammatory biomarkers, suggesting a chronic, low-grade inflammatory response. Interestingly, other authors have shown that dietary supplementation with soluble fiber and pectin alleviates LPS-induced sickness behavior in mice. Such dietary intervention resulted in the redirection of peripheral macrophages toward the M2 functional phenotype [49].

Lastly, the primary sources of non-resolving inflammation in depressive patients may be represented by chronic psychosocial stress or early-life stressful events [2, 16]. These conditions have been shown to induce inflammatory signaling pathways both in peripheral macrophages and in microglia. In particular, stress can prime microglia for subsequent exposure to a similar stressor. These primed cells may persist in a pre-activated state for a long time and respond excessively to even slight stimuli [23].

Currently, depression is frequently regarded as a chronic dysfunction of the immune system with a prevalence of a low-grade inflammatory state [15, 27, 32]. However, it is important to note that despite numerous clinical and experimental data corroborating this claim, the immunological aberrations in a course of depression are variable, and some depressed patients show no detectable changes in immune measures. These findings indicate that the immune system plays an important role in the pathology of depression, although it cannot be regarded as the sole etiological mechanism.

Effect of antidepressive treatments on macrophages

The majority of currently used antidepressant drugs act on the monoamine and serotonin neurotransmitter systems. As pro-inflammatory cytokines are crucially involved in the pathology of depression, one can anticipate that antidepressive treatments will exert an inhibitory effect on their production by the cells of the immune system. Indeed, numerous studies have documented that antidepressants possess anti-inflammatory or immunosuppressive properties, regardless of their type [19]. *In vitro* studies, which have primarily been conducted on peripheral blood mononuclear cells, have revealed that antidepressant drugs generally decrease the release of pro-inflammatory cytokines, and many reports have also shown an increase in the synthesis of anti-inflammatory or suppressive cytokines. Similar effects were noted when cells were collected from depressive patients and cytokine synthesis was assessed *ex vivo* as an effect of antidepressive therapy. Animal studies have also demonstrated, in general, the anti-inflammatory or immunosuppressive action of antidepressants, concurrent with improving depression-like states. Even so, divergent and even contradictory results were obtained in studies of cytokine levels in the circulation of depressed patients. However, in these assessments, antidepressants appeared to normalize the serum levels of major inflammatory cytokines [19].

Studies on the effects of antidepressive treatments on macrophage activity, including microglia and peripheral macrophages, are less common. *In vitro* experiments illustrated that antidepressant drugs with diverse mechanisms of action suppressed TNF-α and NO production by an LPS-stimulated immortalized murine microglial cell line [55], inhibited the secretion of IL-1β and TNF-α in rat mixed glial and microglial cell cultures [37], decreased IFN-γ-induced microglial production of IL-6 and NO [17] and decreased the release of IL-1β, TNF-α and NO as well as the amino acids glutamate and D-serine by LPS-activated microglia [8]. These results indicate a potent anti-inflammatory action of antidepressants on microglia, and such effects may be related to their therapeutic properties. Moreover, a non-pharmacological antidepressive treatment, electroconvulsive shock (ECS), which is an animal model of electroconvulsive therapy (ECT), has also been shown to affect microglia. Jinno and Kosaka [22] showed that ECS induced a decrease in the density of fine microglial branches in the hippocampus of mice, and these changes persisted for one month after the termination of chronic treatment. Others [21] have reported similar signs of microglial activation together with enhanced expression of activation markers. The same authors observed the accu-

mulation of monocyte-derived macrophages within the brain vasculature [20]. The significance of these changes is unclear, but it is supposed that they may be related to the therapeutic action of the treatment.

Regarding the effects of antidepressive treatments on peripheral macrophages, only a few studies have been reported. Belowski et al. [3] showed decreased cytotoxic activity of splenic macrophages obtained from rats that were chronically administered antidepressants. Other authors have investigated the effects of a 7-day period of tryptophan administration on phagocytic activity and the synthesis of ROS by peritoneal macrophages [48]. They showed that this treatment increased phagocytosis and decreased oxidative metabolism in macrophages. These results suggest that both antidepressants and enrichment with serotonin precursors result in an increased phagocytic ability in parallel with decreased cytotoxic potential. Such features are characteristic of anti-inflammatory, M2 macrophages [5].

An experiment conducted in our laboratory revealed that chronic ECS decreased NO synthesis and increased arginase activity in peritoneal macrophages without inducing changes in other signs of metabolic activity [43, 44]. These results suggest the redirection of peripheral macrophages toward the anti-inflammatory M2 phenotype. Similar effects were observed in rats acutely treated with a combination of antidepressants, including fluoxetine and the NMDA receptor antagonist amantadine. Such a combination induced an antidepressant-like effect and also increased the arginase activity to NO synthesis ratio in macrophages, again suggesting a functional shift toward the M2 type [45]. In another experiment effects of the acute administration of fluoxetine and an atypical antipsychotic, risperidone, on peritoneal and pleural macrophages were examined [42]. In that study, both fluoxetine and combined treatment altered the properties of peritoneal and pleural macrophages, as demonstrated by increased an arginase activity to NO synthesis ratio. Additionally, a partial dissociation of the anti-depressive actions and the effects on macrophage activity of the anti-depressants was observed. These findings indicate that the drug-induced effects on macrophages may not be so closely related to their antidepressant-like actions or that their effects on macrophages are secondary to those induced in the neuroendocrine system.

It may be concluded that antidepressants, combined treatment with antidepressants and other drugs as well as non-pharmacological antidepressive treatment (ECS) can all affect the functional properties of peripheral macrophages and skew them toward the anti-inflammatory M2 phenotype. Because macrophages can affect the outcome of inflammatory diseases [13, 14], alleviate sickness behavior [49] and improve cognitive function [7], it is possible that the effects of antidepressive treatments may be, at least in part, mediated by changes in macrophage activity. However, the mechanisms of such a functional shift and its therapeutic significance remain to be elucidated.

Modulation of macrophage functions as an antidepressive treatment

Anti-inflammatory agents, e.g., cyclooxygenase inhibitors [36], pleiotropic antibiotics, minocycline [53] and the TNF-α inhibitor etanercept [56], have been used as adjunctive treatments in antidepressive therapy. However, no specific, macrophage-oriented antidepressive approach has been adopted. A clue with respect to this topic may be provided by a report by Derecki et al. [7]. They showed that bone marrow-derived macrophages that were skewed *in vitro* to the M2 phenotype and transferred intravenously to mice devoid of an adaptive immune system substantially improved the cognitive functions of the recipient mice. The transferred cells localized in the meninges and the peripheral organs and redirected the host's macrophages to the M2 phenotype. Similarly, a study by Sherry et al. [49] showed that non-invasive dietary intervention can skew the macrophage phenotype to M2 and subsequently alleviate sickness behavior. These reports are in line with the supplementary and prophylactic, non-pharmacological treatments of depression, including dietary supplementation with ω-3 polyunsaturated fatty acids [38] and physical activity [11]. Therefore, the positive effects of macrophages in the context of their antidepressive action, contrary to their negative effects, are poorly recognized and may be a promising direction for future studies.

Acknowledgment:
This work was supported by grant no. POIG.01.01.02-12-004/09, which was co-financed by the European Regional Development Fund.

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Received: August 13, 2013; **accepted:** August 30, 2013.