REVIEW ARTICLE

Pathophysiology of major depressive disorder related to the relationship between inflammation and the nervous system

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Abstract

Major depressive disorder (MDD) is a leading cause of disability. It is associated with the highest disability-adjusted life year (DALY) value among all diseases and disorders, placing a significant burden on society. Thus, new advances in treatment methods based on the pathogenesis of MDD are strongly required. Historically, the monoamine hypothesis has been the major theory of depression, but it is too simplistic. It cannot explain the latency of response in the therapeutic action of antidepressants, and up to 30% of depressed patients fail to achieve remission despite multiple treatment trials. Over the past three decades, research has suggested that inflammatory processes are involved in the onset and maintenance of MDD; the inflammatory hypothesis has been proposed. This review will highlight the association between inflammation and the nervous system and the role of inflammation in the pathogenesis of MDD, including whether chronic stress (e.g., psychosocial stress) activates the inflammatory response, what kind of upstream neurogenic processes translate physiologic stress into inflammatory responses, communication pathways, or mechanisms by which the peripheral immune system can influence the brain and behavior; and the pathophysiology by which inflammation affects the nervous system and leads to MDD. Once cytokine signals reach the brain, they can interact with every pathophysiologic domain relevant to mood regulation, which includes neurotransmitter function, hypothalamic–pituitary–adrenal (HPA) axis activity, neural plasticity, and alteration of brain circuitry. Recent data demonstrating the importance of cytokines as biomarkers will also be presented.

Key words: *Major depressive disorder, Depression, Inflammatory system, Cytokines, Interleukin-6*

INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability. It is associated with the highest disability-adjusted life year (DALY) value among all diseases and disorders, placing a significant burden on society (Ferrari, 2010). Thus, new advances in treatment methods based on the pathogenesis of MDD are strongly required. However, the biological mechanisms of MDD are incompletely understood (Ménard, 2015). Historically, the monoamine hypothesis has been the major theory of depression. It postulates a deficiency in serotonin (5-HT) or noradrenaline (NA) neurotransmission in the brain. Findings in patients with depression that support the monoamine hypothesis include several lines of supporting evidence (Belmaker, 2008). Available antidepressant medications, which largely target monoamine pathways, are effective. However, the classical monoamine hypothesis is simplistic; it does not explain the temporal delay in the therapeutic action of antidepressants (Racagni, 2008). If antidepressants work according to the monoamine hypothesis, they should be rapidly effective, but antidepressants generally need 2–4 weeks to have a therapeutic effect on depressive symptoms. Moreover, up to 30% of patients with MDD fail to achieve remission despite multiple treatment trials (Rush, 2007). Hence, identification of novel pathophysiological pathways other than monoamine deficiency that are relevant to MDD is heavily required to reveal neurobiological targets for the development of new medications.

Research over the past three decades has suggested that inflammatory processes are involved in the onset and maintenance of MDD. The inflammatory hypothesis has been proposed (Smith, 1991; Maes, 1993; Sluzewska, 1996). In recent years, the association between inflammation and MDD has been investigated with growing interest (Vogelzangs, 2013; Dantzer, 2007; Kopschaina, 2017; Kim, 2007; Leonard, 2012).

Although mood disorders may have complex pathophysiology and heterogeneous etiologies, increased inflammation is thought to be involved in the disease process and contributes to discrete symptomology, at least in some subsets of patients. However, the underlying mechanisms of inflammation and depressive symptoms remain far from being fully elucidated. This review highlights the association between inflammation and the nervous system as well as the role of inflammation in the pathogenesis of MDD. Recent data demonstrating the importance of cytokines as biomarkers are also presented.

INFLAMMATORY FEATURES OF MDD

The link between MDD and inflammation was initially suggested in the macrophage hypothesis (Smith, 1991), which states that pro-inflammatory cytokines produced by activated macrophages play a role in many symptoms of depression. Nowadays, mounting data indicate a link between inflammation and the pathogenesis of MDD. First, in clinical studies, inflammatory features of MDD have been observed in medically ill and medically healthy patients with MDD. Compared with individuals without MDD, levels of pro-inflammatory cytokines are elevated in the peripheral blood and cerebrospinal fluid (CSF) of patients with MDD (Raison, 2006; Joshua, 2014). Moreover, treatment with antidepressants attenuates cytokine production and action (Barden, 1999; Castanon, 2002; Schiepers, 2005). Plasma levels of some cytokines that are higher during ongoing depression normalize after recovery (Kenis, 2002). Second, the link between inflammation and MDD is supported epidemiologically by the high rate of clinical psychological changes that resemble the characteristics of depression such as anxiety, fatigue, psychomotor slowing, anorexia, cognitive dysfunction, and sleep impairment, observed during pro-inflammatory conditions like obesity, myocardial infarction, ongoing hepatitis C therapy that activates the immune system, and autoimmune disease (Van Gool, 1999; Weinblatt, 1999; Musselman, 2001; Raison, 2005; Bogna, 2019; Marrie, 2017). Third, many human and animal studies have demonstrated that the activation of peripheral innate cytokine pathways, including both peripheral innate immune challenge and acute or chronic stress, leads to increased pro-inflammatory cytokine production and decreased neurotrophic support and neurogenesis in brain areas important to behavior and cognition, which eventually induce psychiatric symptoms (Dantzer, 2001; Koo, 2008; Ben Menachem-Zidon, 2008; Dowlati, 2010; Barrientos, 2003; Wu, 2007; Rodrigues, 2018). Fourth, neurobiological and immunological mechanisms underlying how inflammation targets neurotransmitters and neurocircuitry to change behavior have been elucidated (Felger, 2017).

Psychiatric symptoms induced by inflammatory stimuli mentioned above, referred to as sickness behavior, share many overlapping features with symptoms of depression (Kent,1992). These symptoms can be reliably reproduced by the administration of pro-inflammatory cytokines separately or by treatment with cytokine inducers such as endotoxin and lipopolysaccharide (LPS) or infectious agents such as *Salmonella typhi* and Bacille Calmette-Guerin (BCG) vaccine, an attenuated form of *Mycobacterium bovis* (Yirmiya, 1999; Simen, 2006; Brydon, 2008; Harrison, 2009a, 2009b; O'Connor, 2009). When LPS is administered peripherally, cognitive impairment and increased hippocampal concentrations of tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) occur, which are associated with decreased hippocampal expression of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase B, as well as reduced hippocampal neurogenesis (Dantzer, 2001; Wu, 2007). Further supporting the notion that pro-inflammatory cytokines are the key mediators of sickness behavior, administration of cytokine antagonists such as IL-1 receptor antagonist (IL-1ra) or anti-inflammatory cytokines such as interleukin 10 (IL-10) can block the behavioral effects of treatment with IL-1β, LPS, or both in laboratory rodents (Kent, 1992; Bluthe, 1995; Avitsur, 1997; Dantzer, 2008).

PRO-INFLAMMATORY CYTOKINES AS POTENTIAL BIOMARKERS OF MDD

The heterogeneous nature of MDD requires objective characterization, including assessment of symptoms, severity, and treatment response, for identifying subclasses of MDD (Schmidt, 2011). However, clinical features alone are not sufficient to guide precise decision-making regarding medications suitable for each subtype of MDD. Therefore, biomarkers are needed to facilitate MDD characterization. Blockade of cytokines by antibodies specific for interleukin 6 (IL-6) or TNF-α that do not cross the blood–brain barrier (BBB) has been shown to reduce depressive symptoms in patients with medical

illnesses, including rheumatoid arthritis, psoriasis, and cancer, as well as in patients with MDD (Sun, 2017; Abbott, 2015; Tyring, 2006). These findings indicate that peripheral inflammatory responses may serve as biomarkers and clues to the immunological mechanisms of inflammation in MDD.

Regarding biomarkers, TNF-α and IL-6, which mediate the innate immune response, have been reported to be elevated in MDD. They appear to be biomarkers in MDD. C reactive protein (CRP) has also been found to be elevated in MDD (Zorilla, 2001; Howren, 2009; Dowlati, 2010). There are some inconsistent findings regarding IL-1β (Dowlati, 2010) and various other cytokines (Dahl, 2014).

An association between inflammatory markers and individual depressive symptoms such as fatigue, cognitive dysfunction, and impaired sleep have been described (Meyers, 2005; Motivala, 2005; Bower, 2002). As to treatment responsiveness, a substantial proportion of patients with MDD are treatment-resistant to antidepressants (Bschor, 2012; Rush, 2006). Patients with treatment-resistant depression (TRD) have significantly higher serum levels of soluble IL-6 receptor (sIL-6R) than patients in remission. By contrast, serum levels of IL-6 and TNF-α are similar in patients with TRD and patients in remission. Therefore, sIL-6R may be a useful biomarker for the identification of treatment-resistant MDD (Yamasaki, 2019). On the other hand, CRP was increased in association with TRD associated with other clinical manifestations in MDD, including obesity, vegetative symptoms of fatigue and sleep disturbance, state anxiety, and a history of childhood adversity (Chamberlain, 2019).

PERIPHERAL CYTOKINE RESPONSE TO PERSISTENT STRESS

Even though the inflammatory process is associated with the pathophysiology of MDD, nascent inflammatory processes secondary to evolving medical pathologies, especially in presumably medically healthy individuals, remain to be considered. Sources of immune activation that may contribute to increased inflammation in psychiatric patients who are otherwise medically stable include sleep disturbance, diet, increased gastrointestinal permeability, obesity, and other lifestyle factors such as smoking (Berk, 2013). However, MDD is often related to the normal emotions of sadness and bereavement. Nowadays the most significant causal agent of MDD is chronic social stress (Kendler, 1999). Historically, classic severe states of depression often have no external precipitating cause (Kuhn, 1958), albeit it is difficult to distinguish depression with psychosocial precipitating events from other types (Wakefield, 2007). Therefore, the next question is whether chronic stress (e.g., psychosocial stress) involved in the occurrence of MDD activates the inflammatory response in the periphery and brain. Supporting the association between stress and an inflammatory response, increased expression of pro-inflammatory cytokines was observed in the brains and spleens of rats with sickness behavior that were exposed to chronic stress (You, 2011). In humans, peripheral blood mononuclear cells from healthy volunteers exposed to public speaking and a mental arithmetic stressor had a significant increase in transcription factor nuclear factor κB (NF-κB) DNA binding (Bierhaus, 2003). NF-κB and IL-6 responses to psychosocial stress have been shown to be exaggerated in patients with MDD, consistent with findings that depressive symptoms are associated with amplified IL-6 responses to antigenic challenge (Pace, 2006; Glaser, 2003). Furthermore, chronic stress, including caregiving, marital discord, and perceived stress, is associated with increases in the acute phase protein CRP as well as IL-6 and other inflammatory mediators (McDade, 2006; Kiecolt-Glaser, 2005; Miller, 2008). Of note, adults who were maltreated as children have increased peripheral blood CRP levels compared with adults who had not been maltreated as children (Danese, 2007).

The next question is how neural sensitivity to psychosocial stress relates to inflammatory responses. In other words, what kind of upstream neurogenic processes translate physiologic stress into inflammatory responses? These processes can close the theoretical gap between stress and its influence on immune function.

First, research has shown that psychosocial stress (McEwen, 1998) in animals and humans is perceived in the emotion-related forebrain regions of the corticolimbic system (neurocircuitry related to threat or anxiety) including the amygdala; anterior cingulate cortex (ACC), especially the dorsal ACC (dACC); anterior insula; and periaqueductal gray. Interestingly, the dACC has been shown to play an important role in error detection and conflict monitoring (Carter, 1998). Increased activity in this brain region has been shown to be associated with high trait anxiety, neuroticism, obsessive-compulsive disorder, and bipolar disorder (Eisenberger, 2004). Recently, psychosocial stress signals from the emotion-re-

lated forebrain regions were revealed to activate a vesicular glutamate transporter 1–positive glutamatergic pathway from the dorsal peduncular cortex and dorsal tenia tecta (DP/DTT) to the dorsomedial hypothalamus (DMH), a hypothalamic autonomic center (Kataoka, 2020). The DP/DTT–DMH pathway appears to constitute a psychosomatic connection through which stress and emotions affect the autonomic and behavioral motor systems.

The next mechanism is stress-induced activation of peripheral immune responses by the central nervous system (CNS). The immune system is under the direct control of the autonomic nerves. Activation of the sympathetic nervous system (SNS) leads to the release of NA from SNS nerve fibers into primary and secondary lymphoid organs (Johnson, 2005; Kenney, 2014), other major organ systems (e.g., the vascular system and perivascular tissues), and many peripheral tissues in which pro-inflammatory reactions occur. SNS nerve fibers can also stimulate the adrenal glands to release stored adrenaline (AD) into the systemic circulation. Both of these neuromediators can enhance IL-1β and IL-6 responses and gene expression (Eisenberger, 2012). Stimulation of both α-adrenergic and β-adrenergic receptors activates inflammatory signaling pathways, including the NF-κB pathway (Bierhaus, 2003).

On the contrary, the parasympathetic nervous system (PNS) may play a role in autonomic regulation of inflammation. For example, studies have shown that stimulation of efferent vagus nerve fibers can inhibit cytokine responses to endotoxin in laboratory animals (Pavlov, 2005; Czurua, 2003). These effects are mediated in part by the release of acetylcholine, which inhibits NF-κB activation when bound to the α7 nicotinic acetylcholine receptor (Pavlov, 2005). In humans, heart rate variability in young adults is strongly and inversely related to IL-6 and CRP, consistent with the finding in animals that increased inflammatory markers (e.g., CRP and IL-6) are associated with decreased parasympathetic activity, supporting the notion that the inhibitory effects of PNS activity on innate immune responses extend to humans (Sloan, 2007).

On the other hand, activation of the Nod-like receptor pyrin-containing 3 (NLRP3) inflammasome appears to bridge the gap between exposure to stress and immune activation. Preclinical and clinical studies have demonstrated a link between the assembly of the NLRP3 complex and subsequent proteolysis, leading to the release of the pro-inflammatory cytokines IL-1β and interleukin 18 (IL-18) in chronic stress models and in patients with MDD (Kaufmann, 2017).

PATHOGENESIS OF MDD CAUSED BY PRO-INFLAMMATORY CYTOKINES

The peripheral immune system can influence the brain and behavior through various communication pathways or mechanisms. It remains unclear whether activation of inflammatory pathways in the CNS during depression originate primarily in the periphery, CNS, or both, and whether stress or other processes directly induce inflammation responses within the brain. Indeed, peripheral cytokines are hydrophilic and it seems to be difficult for them to pass their signal to the brain because of their relatively high molecular weight. However, several communication pathways between the periphery and the brain have been postulated, including (1) passage through leaky regions in the BBB in the circumventricular organs (Katsuura, 1990; Esposito, 2001; Pan, 2003; Menard, 2017); (2) active uptake of cytokines across the BBB (Banks, 1995, 2002, 2010); and (3) local actions at peripheral afferent nerve fibers (e.g., vagus nerve) that relay cytokine signals to relevant brain regions, including the nucleus of the solitary tract and hypothalamus (Dantzer, 2008; Miller, 2009). Furthermore, (4) peripheral monocytes are recruited into the brain by CC-chemokine ligand 2 (CCL2; also known as MCP-1), which is produced by microglia when the brain is stimulated by pro-inflammatory cytokines, notably TNF-α (D'Mello, 2009, 2015). At the same time, cytokine-stimulated astrocytes may also be major producers of chemokines such as CCL2 and CXC-chemokine ligand 1 (CXCL1), which attract immune cells to the brain (Hennessy, 2015). The monocytes traffic to the brain in the context of social defeat stress, inducing depressive and anxiety behaviors, whereby monocytes coalesce in several regions of the brain (e.g., amygdala) associated with the detection of threat (Hodes, 2014; Wohleb, 2011, 2012, 2014). Blockade of monocyte infiltration into the brain using antibodies specific for the adhesion molecules P-selectin and α4 integrin abrogated depression-like behavior in an animal model (D'Mello, 2009). These monocytes traffics primarily to perivascular and meningeal spaces, leading to activation of endothelial cells responsible for the subsequent release of second messengers (e.g., prostaglandin E2 and nitric oxide) that act on specific brain targets (Capuron, 2011).

The peripheral inflammatory system can affect the CNS, which leads to MDD. Once cytokine signals reach the brain, they can interact with virtually every pathophysiologic domain relevant to mood regulation. These include effects on neurotransmitter function, hypothalamic–pituitary–adrenal (HPA) activity, neural plasticity, and alteration of neurocircuitry. Of note, stress-induced activation of the cytokine response in the CNS appears to be largely dependent on the activation of microglia (Frank, 2007) (Figure 1). CCL2 released by astrocytes and endothelial cells primes microglia to produce IL-1β and TNF-α. On the other hand, IL-6 is known to participate in neurogenesis (influencing both neurons and glia cells) and responses by mature neurons and glial cells under normal conditions. IL-6R is restricted to some tissues, while gp130 is ubiquitous. sIL-6R, which is formed physiologically, can bind both IL-6 and gp130. This is followed by signaling in cells with or without endogenous IL-6R expression, a mechanism known as trans-signaling pathway (Jones, 2001). Inhibition of the IL-6 trans-signaling pathway in the brain facilitates recovery from LPS-induced sickness behavior (Burton, 2011). The IL-6 signal is transduced to microglia through trans-signaling to change expression of IL-6, IL-1β, and IL-10 (Garner, 2018), suggesting that trans-signaling pathway is involved in the onset of MDD (Yamasaki, 2019).

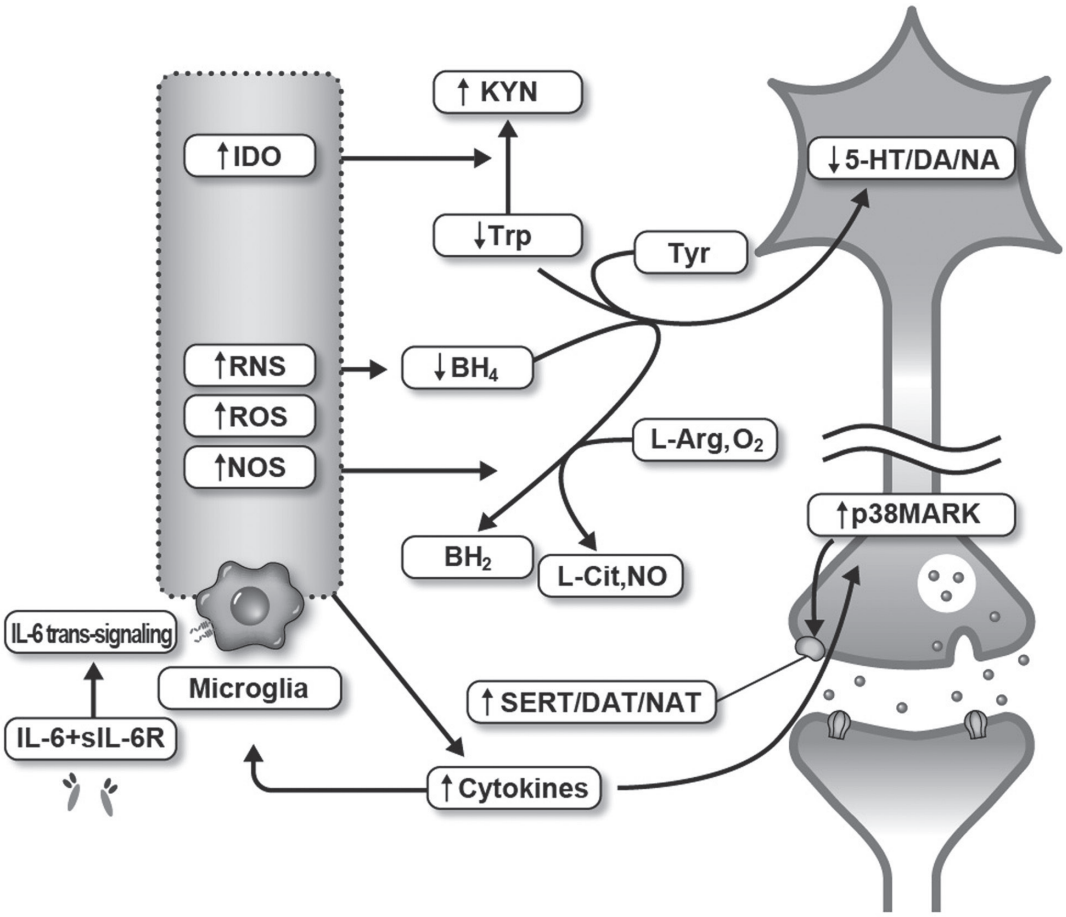

Figure 1. Effects of cytokines on neurotransmitter function
Pro-inflammatory cytokines including interleukin 1β (IL-1β), IL-6, tumor necrosis factor α (TNF-α), interferon α (IFN-α), and IFN-γ can activate indoleamine 2,3-dioxygenase (IDO), which is a rate-limiting enzyme in tryptophan metabolism. Tryptophan is the primary precursor of serotonin. When tryptophan is metabolized to kynurenine (KYN), biosynthesis of serotonin is decreased. The IL-6 signal transduced to microglia through trans-signaling changes the expression of IL-6, IL-1β, and IL-10. Pro-inflammatory cytokines also decrease levels of tetrahydrobiopterin (BH4), enzymatic cofactors for monoamine synthesis, which is highly sensitive to cytokine-induced reactive nitrogen species (RNS) and reactive oxygen species (ROS). In addition, pro-inflammatory cytokines can induce production of nitric oxide (NO) by NO synthase (NOS) from L-arginine (L-Arg). This process can usurp available BH4, resulting in decreased DA and NA availability. Cytokines also activate p38 mitogen-activated protein kinase (p38 MAPK), thereby increasing the expression and function of the presynaptic transporters for 5-HT, DA, and NA. BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; DA, dopamine; DAT, dopamine transporter; 5-HT, serotonin; IDO, indoleamine 2,3-dioxygenase; KYN, kynurenine; L-Arg, L-arginine; L-Cit, L-citrulline; NA, noradrenaline; NAT, noradrenaline transporter; NO, nitric oxide; NOS, NO synthase; p38MARK, p38 mitogen-activated protein kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SERT, serotonin transporter; sIL-6R, soluble interleukin 6 receptor; Trp, tryptophan.

EFFECTS OF CYTOKINES ON NEUROTRANSMITTER FUNCTION

Once cytokine signals reach the brain, microglia are activated. This activation initiates an inflammatory cascade whereby release of relevant cytokines, chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS, respectively) induces activation of astrocytes, thereby amplifying inflammatory signals within the CNS (Miller, 2009). Pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, as well as interferon α (IFN-α) and IFN-γ from T cells, induce indoleamine 2,3-dioxygenase (IDO), which metabolizes tryptophan, the primary amino acid precursor of 5-HT, into kynurenine (KYN). This process results in decreased 5-HT synthesis (Capuron, 2002, 2003). Several studies have documented that activation of IDO in the brain plays a critical role in the development of depression-like behavior in rodents (Lestage, 2002; O'Connor, 2009). In addition, cytokines activate p38 mitogen-activated protein kinase (p38 MAPK), which strongly upregulates the expression of presynaptic membrane reuptake pumps (transporters) for 5-HT, NA, and dopamine (DA) (Zhu, 2005, 2006). On the other hand, cytokine-induced increases in inducible nitric oxide synthases (NOS) activity can usurp available 5,6,7,8-tetrahydrobiopterin (BH4), which is a cofactor for several aromatic amino acid hydroxylases and thus strongly involved in the biosynthesis of 5-HT, DA, and NA. Tyrosine hydroxylase is the rate-limiting enzyme in DA synthesis and Tyrosine hydroxylase leads to lower DA and NA availability (Cunnington, 2010; Xia, 1998). Furthermore, cytokines trigger high output of RNS and ROS by microglia, which can destroy oxidation-labile BH4. Oxidative loss of BH4 in chronic inflammatory conditions can reduce the biosynthesis of catecholamines, which may be related to disturbed adrenergic neurotransmitter pathways in patients (Neurauter, 2008).

EFFECTS OF CYTOKINES ON THE HPA AXIS

Some of the effects of cytokines on mechanisms relevant to MDD involve the HPA axis (Besedovsky, 1996), which plays a pivotal role in stress responses in mammals. In the HPA, stress promotes the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH promotes the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH promotes the secretion of glucocorticoids (GCs) from the adrenal gland, which leads to higher GC levels in the blood and CSF. Elevated GC levels suppress the secretion of CRH via GC receptors (GRs) in the hippocampus, which is known as the negative feedback loop in the HPA axis. One pathway by which cytokines may influence HPA axis function is by impairing this negative feedback regulation, leading to decreased responsiveness to GC, that is, GC resistance. GC resistance is manifested by reduced sensitivity to the inhibitory effects of dexamethasone (DEX) on the production of ACTH and GCs during the DEX suppression test and the DEX-CRH test (Pariante, 2001). This GC resistance is mediated, in part, by alterations in GRs (Pariante, 2001). Cytokine activation of relevant inflammatory signaling molecules, including NF-κB, p38 MAPK, and signal transducer and activator of transcription 5 (STAT5), inhibit GRs through disruption of GR translocation from the cytoplasm to the nucleus, as well as through nuclear protein–protein interactions that inhibit GR-DNA binding (Pace, 2007). These interactions lead to higher GC levels and reduced neural plasticity, causing MDD (Sigalas, 2012). Cytokine-induced activation of IDO may also be involved in the attenuation of negative feedback inhibition of circulating GCs in the HPA axis through the production of quinolinic acid (QUIN), which is hypothesized to cause hippocampal atrophy and GR loss (Wichers, 2004).

EFFECTS OF CYTOKINES ON NEURAL PLASTICITY

Neural plasticity is believed to play a fundamental role in the maintenance of neural integrity, which includes neurogenesis, long-term potentiation, and dendritic sprouting. Especially in the hippocampus, reduced neurogenesis in the adult dentate gyrus (Gould, 1992; Cameron, 1993) is a hallmark of chronic exposure to stress in laboratory animals (Duman, 2006). Cytokines, including IL-6, TNF-α, and IL-1β, can activate microglia to convert KYN into QUIN, a potent N-methyl-d-aspartate receptor (NMDAR) agonist and stimulator of glutamate (Glu) release from astrocytes (Müller, 2007). Multiple astrocyte functions are also compromised by excessive exposure to QUIN and cytokines, which ultimately leads to downregulation of Glu transporters and impaired Glu reuptake. This, in turn, can lead to excessive Glu. Of note, Glu released by astrocytes has preferential access to extrasynaptic NMDARs, which mediate excitotoxicity and decreased production of trophic factors including BDNF, ultimately disrupting neural plasticity through excitotoxicity and apoptosis

and leading to depression (Harry, 2012; Hashimoto, 2013; Hardingham, 2002, 2010) (Figure. 2).

On the other hand, several studies have shown that blockade of IL-1β through the administration of IL-1ra, transplantation of IL-1ra–secreting neural precursor cells, or IL-1 knockout in mice, reverses the decrease in BDNF production and neurogenesis associated with chronic stress while also reversing stress-induced behavioral changes (Ben Menachem-Zidon, 2008; Goshen, 2008; Koo, 2008).

Cytokines can also lead to the release of RNS and ROS from microglia and astrocytes, which, in combination with QUIN, amplify oxidative stress and further endanger neurons and oligodendrocytes, which are especially vulnerable to oxidative damage (Schwarcz, 2002; Rios, 1991; Gavillet, 2008; Matute, 2006;

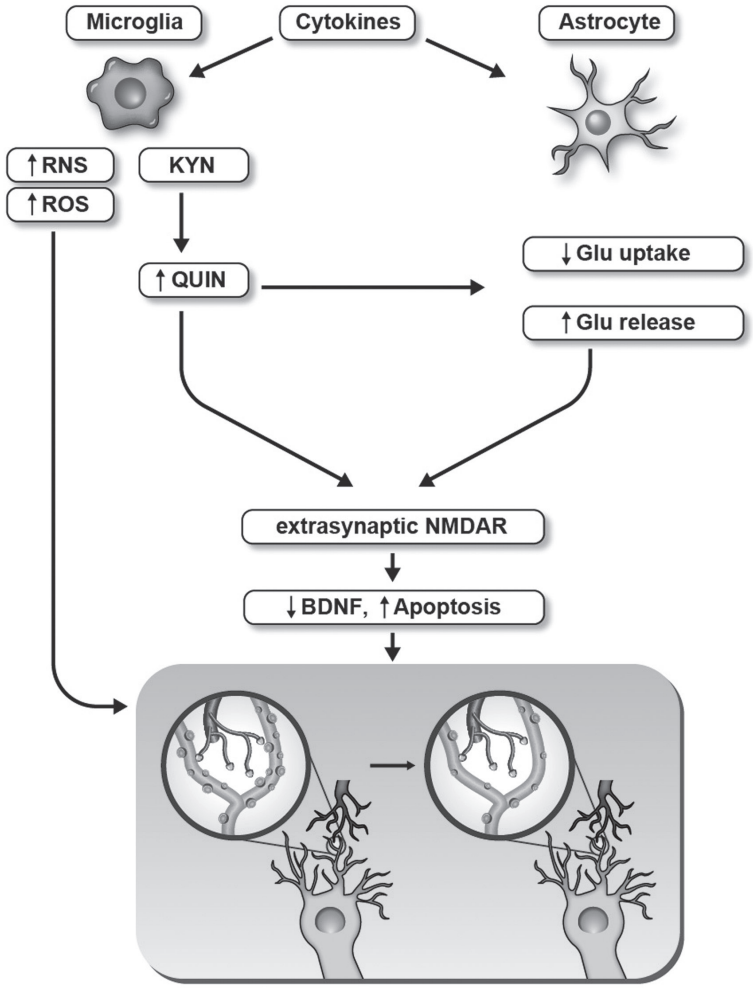

Figure 2. Effects of cytokines on neural plasticity
Pro-inflammatory cytokines, including interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and IL-1, can activate microglia to convert kynurenine (KYN) into quinolinic acid (QUIN), which is a potent N-methyl-d-aspartate (NMDA) receptor agonist and stimulator of glutamate release from astrocytes. QUIN, together with cytokines, downregulate glutamate transporters and impair glutamate reuptake by astrocytes, which in turn can lead to excessive glutamate. Glutamate released by astrocytes has preferential access to extrasynaptic NMDA receptors (NMDARs), which mediate excitotoxicity and decreased production of trophic factors including brain-derived neurotrophic factor (BDNF). This ultimately disrupts neural plasticity through excitotoxicity and apoptosis, affecting neurogenesis, long-term potentiation, and dendritic sprouting. Cytokines can also induce RNS/ROS release from microglia and astrocytes, which amplify oxidative stress in combination with QUIN, further endangering neurons and oligodendrocytes, which are especially vulnerable to oxidative damage. BDNF, brain-derived neurotrophic factor; Glu, glutamate; KYN, kynurenine; NMDAR, N-methyl-d-aspartate receptor; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species.

McTigue, 2008; Ida, 2008; Buntinx, 2004; Li, 2008; Thornton, 2006).

CYTOKINE EFFECT ON NEUROCIRCUITRY

Functional magnetic resonance imaging (fMRI) studies have demonstrated that increased activation of threat-related and anxiety-related neurocircuitry, which includes the dACC, insula, and amygdala, is associated with increased inflammation. For example, the dACC is significantly activated in patients receiving IFN-α for hepatitis C treatment compared with control subjects not receiving IFN-α (Capuron, 2005). These data are consistent with the fact that positron emission tomography using *N*-(2-(2-fluoroethoxy)benzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide labeled with ^{18}F–([^{18F}F]FEPPA), which binds to the translocator protein (TSPO), has revealed that microglia are activated particularly in the prefrontal cortex (PFC), insula, and ACC. Increased TSPO distribution volume in the ACC is correlated with depression severity (Setiawan, 2015). TSPO is an 18-kDa protein located on the outer mitochondrial membrane in microglia. Increased TSPO expression occurs when microglia are activated during neuroinflammation.

On the other hand, depression is recognized to be a multi-componential disorder (Caligiuri, 2000; Morrens, 2007; Pizzagalli, 2014; Zald, 2017). Inability to experience pleasure or reward (anhedonia) is one of the core symptoms of depression (Ebmeier, 2006). Wanting, liking, and learning have been identified as three important dissociable components of reward (Berridge, 2009). In particular, wanting and learning have been linked to dopaminergic neurotransmission in the reward network consisting of the ventral striatum in the basal ganglia (Knutson, 2001; Schott, 2008). Numerous neuroimaging studies have identified that disruption of the basal ganglia is an important action of cytokines. Increased DA uptake and decreased DA turnover in the ventral striatum, caudate, and putamen were demonstrated in a positron emission tomography (PET) study of patients with hepatitis C virus (HCV) infection treated with IFN-α using [^{18}F] fluorodopa (Capuron, 2012). These findings were associated with decreased effort-based motivation and lower activation of reward circuitry in the basal ganglia (Capuron, 2012; Eisenberger, 2010; Felger, 2013). In the first study to examine the functional effects of IFN-α on the brain, in addition to the decreased metabolism in the PFC, increased glucose metabolism was found in the basal ganglia, particularly in the DA-rich putamen (Juengling, 2000), as assessed by PET neuroimaging with fluorine-18–labeled fluorodeoxyglucose (FDG). Next, fMRI also demonstrated that inflammatory stimuli are associated with lower reward responsiveness in the basal ganglia, including the ventral striatum, in otherwise non-depressed patients with HCV infection undergoing IFN-α therapy (Reuter, 2005). Administration of cytokine-inducing endotoxin or typhoid vaccination to healthy volunteers produces similar effects on the ventral striatum in response to rewarding stimuli (Eisenberger, 2010; Harrison, 2015). Typhoid vaccination compared with normal saline placebo has been shown to activate the subgenual ACC (sgACC), a brain region implicated in depression, and decrease connectivity of the sgACC with the ventral striatum, an effect modulated by plasma IL-6 (Harrison, 2009a). These fMRI findings have been extended to patients with depression whose increased plasma CRP and cytokine levels are associated with decreased functional connectivity within the reward circuitry, including the ventral striatum and the ventromedial PFC (vmPFC), which in turn are correlated with increased symptoms of anhedonia (Felger, 2016).

CONCLUSION

Over the past three decades, an intricate interaction among immune activation, release of pro-inflammatory cytokines, and changes in multi-layered aspects of brain function related to mood and behavior has been described. Despite extensive efforts, questions regarding when and how inflammation becomes detrimental remain to be answered. Such incomplete understanding likely arises from the fact that MDD encompasses multiple etiologies and has a highly variable course, inconsistent response to treatment, and no established mechanisms.

In this review, we have attempted to outline the pathophysiological pathways from causes like social stress to MDD that involve peripheral inflammation and neuroinflammation. A latency of response to currently used antidepressants and cases that are refractory to antidepressants are issues with the monoamine hypothesis that may be explained at least in part by the effects of cytokines, i.e., the involvement of reduced monoamine synthesis following activation of IDO and decreases in BH4, increased expression of transporters after p38 MARK activation, reduced neural plasticity due to GC resistance, excitotoxicity due to increased QUIN and excessive Glu binding to the extrasynaptic NMDARs in combination with RNS and ROS, and decreased production of trophic factors including BDNF. On the other hand, the mo-

lecular basis of relationships between the alteration of neurocircuitry and the effect of cytokines remained to be clarified. Currently, data support the hypothesis that the effect of cytokines on neurocircuitry including the dACC, insula, and amygdala may lead to threat and anxiety and that the effects of cytokines on dopaminergic pathways may lead to functional consequences on reward circuitry associated with fundamental alterations in motivation, which contribute to symptoms of anhedonia.

Importantly, only some subgroups of patients with depression have higher levels of inflammatory markers. Anti-inflammatory treatments in patients without inflammation may be detrimental, because TNF blockade with infliximab in patients with lower levels of inflammation impaired the placebo response (Raison, 2013). Thus, not all types of depression might be linked to inflammation (Raison, 2013).

Nevertheless, given the strong need for novel therapeutics based on the high rates of treatment resistance across disorders, studies identifying precise targets for reversing the effects of inflammation are needed. Research on how inflammation affects neurotransmitter function, neuroendocrine activity (e.g., HPA axis), neural plasticity, and alteration in neurocircuitry or other unknown aspects, should be continued. Strategies to prevent depression are also needed.

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