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Review

REVIEW

Inflammation Models of Depression in Rodents: Relevance to Psychotropic Drug Discovery

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Abstract

Inflammation and depression are closely inter-related; inflammation induces symptoms of depression and, conversely, depressed mood and stress favor an inflammatory phenotype. The mechanisms that mediate the ability of inflammation to induce symptoms of depression are intensively studied at the preclinical level. This review discusses how it has been possible to build animal models of inflammation-induced depression based on clinical data and to explore critical mechanisms downstream of inflammation. Namely, we focus on the ability of inflammation to increase the activity of the tryptophan-degrading enzyme, indoleamine 2,3 dioxygenase, which leads to the production of kynurenine and downstream neuroactive metabolites. By acting on glutamatergic neurotransmission, these neuroactive metabolites play a key role in the development of depression-like behaviors. An important outcome of the preclinical research on inflammation-induced depression is the identification of potential novel targets for antidepressant treatments, which include targeting the kynurenine system and production of downstream metabolites, altering transport of kynurenine into the brain, and modulating glutamatergic transmission.

Keywords: Depression, inflammation, glutamate, quinolinic acid, indoleamine 2,3-dioxygenase

Introduction

Activation of the immune system, through either infection or administration of cytokines, causes significant changes in eating, drinking, social, and sleeping behaviors in both rodents (Hart, 1987; O'Reilly et al., 1988; Crestani et al., 1991; Yirmiya, 1996) and humans (Capuron et al., 2002; Vollmer-Conna et al., 2004). Similar behavioral alterations are found in patients with depression. For example, depressed individuals have disturbed sleep patterns (Coble et al., 1979; Pigeon et al., 2004; Armitage, 2007), greater fatigue (Demyttenaere, 2005), fewer social interactions (George et al., 1989), and anhedonia (Pizzagalli et al., 2007; Sherdell et al., 2012). Indeed many of these behavioral alterations are diagnostic criteria for major depression as outlined by the DSM.

The relationship between depression and immunity has been researched for several decades. Initially depression was thought to be associated with a suppression in immunity (Schleifer et al., 1984). Investigators came to this conclusion after finding that blood lymphocytes of depressed individuals had an attenuated proliferative response when stimulated with mitogens (Schleifer et al., 1984; Kronfol et al., 1986; Kronfol and House, 1989). This was associated with reduced natural killer cell activity (Nerozzi et al., 1989). In addition, depressed patients were known to have elevated glucocorticoids, specifically cortisol (Carroll et al., 1976), and a dysfunctional stress feedback system (Carroll et al., 1968). Since glucocorticoids were well known to dampen immune responses (Crabtree et al., 1979), the immunosuppression found in depressed patients seemed logical and corresponded nicely with the endocrine abnormalities. Contrary to the suggestion that depression was immunosuppressive, Smith (1991) proposed the macrophage theory of depression that drew on research demonstrating

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interleukin (IL)-1 can lead to endocrine abnormalities and significantly alter behavior. In addition, inflammation was seen as a common link between depression and other diseases that were often comorbid with depression. In short, Smith's theory proposed that in depressed patients activated macrophages produced cytokines, which lead to depression (Smith, 1991). Soon, evidence began accumulating that depressed patients were actually showing patterns of an activated inflammatory response. Depressed patients were reported to have an increase in leukocytes, monocytes, and other inflammatory factors, including prostaglandins (Ohishi et al., 1988; Maes et al., 1992) and increased NK cells (Seidel et al., 1996). Maes (1995) followed up with his own studies on inflammation and depression and described several ways that inflammation could influence depression, including decreased bioavailability of tryptophan for the synthesis of serotonin. During the same time, animal studies were documenting the relationship between inflammation and sickness behavior (Bluthe et al., 1991, 1992a, 1992b, 1994, 1995; Kent et al., 1992; Nadjar et al., 2005). In addition to reducing motor activity and food intake and increasing slow wave sleep, the cytokine inducers lipopolysaccharide (LPS) (Bluthe et al., 1992a), IL-1 (Kent et al., 1992), and tumor necrosis factor (TNF) (Bluthe et al., 1991, 1994) were found to decrease social interaction in rodents. Importantly, these effects were obtained whether LPS or cytokines were administered at the periphery or in the brain, indicating a possible central site of action for peripheral cytokines. Yirmiya (1996) first reported that endotoxin caused depressive-like behaviors in rodents that were sensitive to the effects of antidepressant drugs.

Since the macrophage theory was proposed, the last 2 decades have seen an abundant amount of investigation into the relationship between inflammation and depression at both the clinical and preclinical levels. Patients with depression are now reported to have elevated levels of inflammatory markers, including proinflammatory cytokines (Kim et al., 2008; Shelton and Claiborne, 2010), C-reactive protein (Danese et al., 2008; Vogelzangs et al., 2012; Morris et al., 2014), and myeloperoxidase (Vaccarino et al., 2008). Although some studies have reported negative results (Carpenter et al., 2004; Basterzi et al., 2005), several meta analyses support the association between depression and proinflammatory cytokines (Howren et al., 2009; Dowlati et al., 2010). Furthermore, the literature indicates that only specific subtypes of depression are associated with inflammation. For example, patients with atypical depression have an increase in plasma C-reactive protein (Hickman et al., 2014), proinflammatory cytokines (Lamers et al., 2013), and leukocyte numbers (Rothermundt et al., 2001) compared with healthy controls or patients with melancholic depression, although one report supports both melancholic and atypical patients having elevated biomarkers of inflammation (Karlovic et al., 2012). Interestingly, atypical depression is also characterized by symptoms of fatigue, hypersominia, and lethargy (Gold and Chorousos, 2002), which match the known behavioral effects of cytokines. Although not all traits of atypical depression align well with sickness behaviors, including weight gain and hypoactivity of the hypothalamic pituitary adrenal system, it is possible that these are due to mechanisms other than inflammation.

Rodent models of depression are also associated with elevated levels of inflammation in the periphery and brain (Grippo et al., 2005; Goshen et al., 2008; You et al., 2011). In addition, Koo and Duman (2008) and Goshen et al. (2008) have demonstrated that cytokine signaling is essential for the development of depressive-like behaviors in stress-based animal models of depression. Further animal research has demonstrated that antidepressants may have antiinflammatory effects (Tynan et al., 2012), and antiinflammatory drugs can prevent depressive-like behaviors (Kreisel et al., 2014). While a complete review of this literature is too large to be completed here, comprehensive reviews of the research on inflammation and depression can be found elsewhere (Felger and Lotrich, 2013; Furtado and Katzman, 2015; Lotrich, 2015; Yirmiya et al., 2015).

Importantly, a direct effect of immune stimulation on mood has been demonstrated in a clinical population. Capuron and Ravaud (1999) report that cancer patients treated with interferon-alpha and/or IL-2 developed depressive-like symptoms, and this has been replicated by others (Bonaccorso et al., 2002; Kraus et al., 2002; Reichenberg et al., 2005). In addition, it has been highlighted that patients afflicted with disorders associated with inflammation, including diabetes, multiple sclerosis, and cardiac disease, show higher rates of depression. Physically ill patients with chronic inflammation have an improvement in mood when given treatments that target inflammatory cytokines, such as the TNF-antagonist infliximab (Tyring et al., 2006; Feldman et al., 2008). Furthermore, rodent studies have confirmed the direct relationship between immune activation and depression. For example, rodents administered proinflammatory cytokines show depressive-like behaviors, such as increased immobility in the forced swim and tail suspension tests and reduced sucrose preference (Brebner et al., 1999; Makino et al., 2000; Dunn and Swiergiel, 2005; Wu and Lin, 2008).

Our research group has focused on understanding inflammation-induced depression and the downstream mechanisms. We have taken great care in developing an animal model of depression that is based on the clinical literature demonstrating that depression develops on a background of sickness behavior (Dantzer et al., 2008). This review will discuss the current state of research on inflammation-induced depression, what is known about the mechanisms, and possible novel targets for the treatment of inflammation-induced depression.

Inflammation-Induced Depression

Inflammation-induced depression can be studied using a variety of inflammatory agents, including LPS, the viral mimetic Poly I:C, and Bacillus Calmette-Guerin (BCG). Treated animals lose weight, eat and drink less, and decrease their motor activity for several hours to days, depending on the nature of the inflammatory agent and dose. These sickness behaviors correspond with elevations in proinflammatory cytokines at the periphery and in the brain (Laye et al., 2000; Parnet et al., 2002; André et al., 2008). In the LPS-induced model of depression, sickness behaviors will typically resolve within 24 hours, whereas BCG inoculation will result in sickness behavior lasting several days (O'Connor et al., 2009a). Interestingly, when sickness behaviors have resolved, the rodents display depressive-like behaviors (Figure 1 for schematic). For example, 24 hours after injection of LPS, when motor activity is back to normal and appetite present, treated animals show increased immobility in the forced swim test and tail suspension test as well as decreased sucrose preference (Frenois et al., 2007; O'Connor et al., 2009c, Sulakhiya et al., 2016; Ge et al., 2015). Sickness and depressive behaviors depend on the initial inflammation, as antiinflammatory agents can attenuate both (Bluthe et al., 1992a; Nadjar et al., 2005; Henry et al., 2008; O'Connor et al., 2009c). Interferon-gamma is a crucial component in this model, as transgenic animals with deletion of its receptor do not show depressive-like behaviors (O'Connor et al., 2009b). Likewise, many laboratories have continued to demonstrate that a variety of antiinflammatory compounds abrogate or attenuate depressive-like behaviors using this model (Ferreira Mello et al., 2013; Ji et al., 2014; Ma et al., 2014; Wang et al., 2014; An et al.,

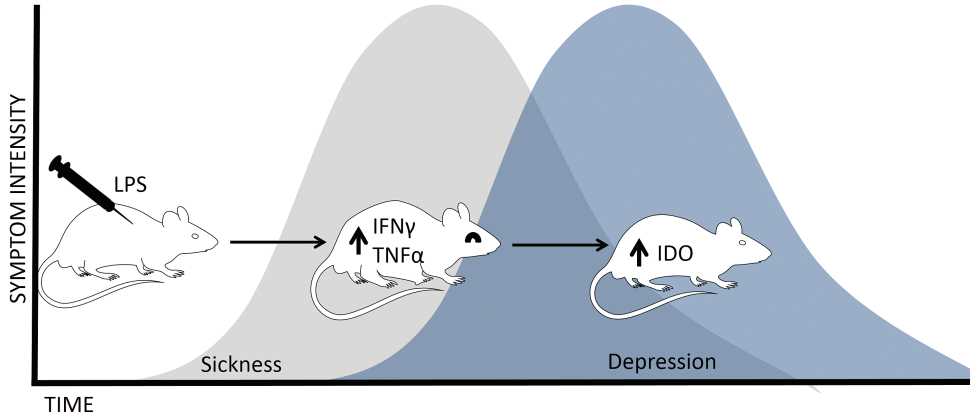

Figure 1. Schematic timeline of lipopolysaccharide (LPS) model of depression. LPS administration increases peripheral cytokines and leads to sickness behaviors, including lack of movement and decrease in food and water intake. Around 24 hours postinjection, rodents begin eating and moving similarly to control animals as their sickness behaviors have resolved. Proinflammatory cytokines will cause an elevation of indoleamine 2,3 dioxygenase (IDO) 24 hours after LPS injection. During the same time that IDO is elevated, animals will be anhedonic and spend more time immobile in the forced swim test.

2015; Ge et al., 2015; Li et al., 2015; Yao et al., 2015; Sulakhiya et al., 2016). In addition, this model has been modified in a variety of ways, including altering inflammatory agents (Fischer et al., 2015), initiating chronic inflammation (Kubera et al., 2013; Adzic et al., 2015; Guan et al., 2015), or combining it with chronic stress exposure (Elgarf et al., 2014) to study depression.

While the primary focus of this review is depressive behaviors, there is a growing literature demonstrating inflammation-induced increases in anxiety-like behaviors in rodents (Salazar et al., 2012; Bassi et al., 2012; Gibney et al., 2013; Baganz et al., 2015; Savignac et al., 2016; Sriram et al., 2016; Sulakhaiya et al., 2016) and humans (Grigoliet et al., 2011; Reichenberg et al., 2001; Lasselin et al., 2016). Sulakhaiya (2016) found that LPS-treated animals have an increase in anxiety-like behavior, as measured by the elevated plus maze. Here, the LPS-treated animals spent more time in the closed arms and a reduction in time spent in the open arms. However, the animals were tested only a few hours after LPS administration, probably still at the peak of the sickness response. Testing behavioral measures of anxiety shortly after LPS injection may confound the results, as the rodents will most likely be moving less due to sickness. However, some papers have demonstrated anxiety behaviors after sickness behaviors have resolved (Salazar et al., 2012; Gibney et al., 2013). Anxiety and depression often appear together in the clinical population (Brown et al., 2001), and modeling both of these symptoms together can both be beneficial and problematic. On one hand, the presence of both anxiety and depression could reflect a more relevant model of depression, but it is difficult to distinguish the contribution of anxiety to depressive behaviors and vice versa.

Healthy human subjects given an inflammatory agent, such as endotoxin or typhoid vaccination, show a significant reduction in mood and increased anxiety (Reichenberg et al., 2001; Wright et al., 2005; Eisenberger et al., 2009, 2010). The reduction in mood is correlated with plasma IL-6 levels (Brydon et al., 2008; Eisenberger et al., 2009) as is fatigue (Brydon et al., 2008). Interestingly, imaging studies found that typhoid vaccination alters neural activity of the cingulate cortex and its connections with other brain areas associated with mood (Harrison et al., 2009). Similarly, Eisenberger et al. (2010) found that endotoxin treatment decreases ventral striatum responding to reward, further supporting that inflammation can alter critical neural circuits involved in depression.

Indoleamine 2,3 Deoxygenase

Insights about mechanisms downstream of inflammation have come from clinical studies that examined the effects of interferon-alpha on mood of cancer and hepatitis C virus-infected patients. In both groups, the development of depressive symptoms was associated with decreased circulating levels of tryptophan (Bonaccorso et al., 2002; Capuron et al., 2002). Furthermore, a significant correlation between variations in tryptophan levels and changes in depression scores was reported. Specifically, the greater the fall in tryptophan levels, the more severe the symptoms of depression as measured by the Montgomery and Asberg depression rating scale (Capuron et al., 2002).

The relationship between tryptophan, serotonin, and depression has a long history in psychiatry. Tryptophan is the precursor of serotonin, and because tryptophan hydroxylase is not saturated by its substrate, the bioavailability of tryptophan regulates the amount of serotonin formed in the brain. Rodents fed a low tryptophan-containing diet show a decrease in serotonin in their brain (Biggio et al., 1974). Similarly, human subjects on a tryptophan-restricted diet have decreased levels of tryptophan and serotonin metabolites in their cerebrospinal fluid (Perez-cruet et al., 1974). Depressed patients have high levels of tryptophan metabolites in their urine (Curzon and Bridges, 1970), and a decrease in tryptophan in the blood and cerebrospinal fluid (Maes et al., 1987, 1993). The depletion of tryptophan alone is also associated with a depressed mood (Young et al., 1985). However, this is only apparent in subjects who are at risk of being depressed either because of a family history of depression or because they are in a remission phase (Riedel et al., 2002). Lastly, tryptophan administration in conjunction with an MAO-inhibitor potentiates the antidepressant drug effect (Coppen et al., 1963), which suggests that tryptophan depletion may be a critical biological component of depression.

Tryptophan is mainly metabolized via the kynurenine pathway (Figure 2), beginning with conversion of tryptophan to kynurenine by 1 of 2 enzymes, primarily tryptophan 2,3, dioxygenase or indoleamine 2,3, dioxygenase (IDO). These enzymes are regionally divided in the periphery but are both found in the brain (Saito et al., 1991; Haber et al., 1993; Alberati-giani et al., 1997). Tryptophan 2,3, dioxygenase predominately metabolizes tryptophan in the liver (Nakamura et al., 1980) and responds to hormonal regulations, such as cortisol and glucagon (Nagao et al., 1986; Nakamuras et al., 1987). IDO is found in a variety of tissues, especially immune cells.

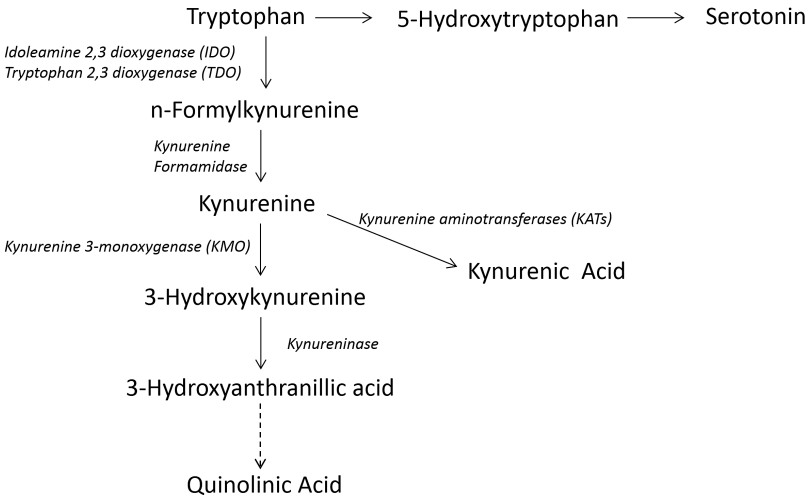

Figure 2. Simplified tryptophan metabolism by the kynurenine pathway. Tryptophan is most commonly metabolized into kynurenine via one of two enzymes: indoleamine 2,3 dioxygenase (IDO) or tryptophan 2,3, dioxygenase. Kynurenine can be further broken down into a variety of metabolites that are neuroactive, including 3-hydroxykynurenine (3HK), quinolinic acid, and kynurenic acid. The conversion from 3-hydroxyanthranillic acid to quinolinic acid, represented by a dashed line, requires 2 reactions. The first is an enzymatic and the other is nonenzymatic. Alternatively, tryptophan can also produce serotonin.

IDO activity is induced by the cytokines interferon-gamma and TNF-alpha (Yoshida et al., 1981; Yoshida and Hayaishi, 1987). LPS administration, HIV infection, or interferon treatment increases metabolites of kynurenine in the periphery, brain (Heyes, 1988; Saito et al., 1991), and CSF (Heyes et al., 1989). The first demonstration of a role for IDO activation was in the field of reproductive immunology. Pregnancy is associated with a significant decrease in tryptophan in the plasma (Schröcksnadel et al., 1996), which is secondary to activation of IDO at the level of the trophoblast. Cytotoxic cells that are involved in the recognition of the trophoblast as antigenic become anergic because of the local depletion of tryptophan (Munn et al., 1998). Therefore, it is possible that an increase in IDO following inflammation could deplete tryptophan, resulting in a decreased serotonin concentration in the brain, and cause depressive-like behaviors.

To test this hypothesis, we used the LPS and BCG model of depression to show that activation of IDO is a late event, which is in agreement with the late development of depressive-like behavior. More specifically, we observed that LPS increased IDO in the brain 24 hours after injection (Lestage et al., 2002) at which time depressive-like behavior become apparent (Frenois et al., 2007). This increase in enzymatic activity of IDO was associated with an increase in the ratio of kynurenine to tryptophan in the periphery and brain 24 hours post LPS (O'Connor et al., 2009c; Walker et al., 2013). Other inflammatory agents, including poly I:C and interferon alpha, cause similar behavioral and biochemical results (Gibney et al., 2013; Fischer et al., 2015). Rats injected with poly I:C have elevated IDO and ratio of kynurenine to tryptophan in the brain (Gibney et al., 2013). Similarly, rats administered recombinant human interferon alpha displayed increased immobility in the forced swim test (Fischer et al., 2015). However, their brain ratio of kynurenine to tryptophan was increased but not significantly ($P < .10$). Imipramine blocked the behavioral effects of interferon but had no effect on the kynurenine to tryptophan ratio. These results are difficult to interpret for several reasons, including the species-specific activity of human interferon alpha. Earlier studies on the behavioral effects of human interferon alpha showed that these are due to activation of brain opioids (e.g., Dafny et al., 1988). Secondly, rats are not a good species for studying IDO activation, because the large quantities of nitric oxide they produce inhibit IDO (Thomas et al., 1994).

To determine if IDO was important, we used pharmacological and genetic tools to demonstrate that activation of this enzyme was necessary for the development of depressive-like behavior, but not sickness behavior. In particular, we found that the IDO inhibitor, 1-methyl tryptophan, blocked the depressive-like behavior but did not significantly alter inflammation or sickness behaviors (O'Connor et al., 2009c). In a similar manner, deletion of the gene coding for IDO, *ido1*, abrogated the development of BCG-induced depression-like behavior (O'Connor et al., 2009a). After demonstrating that IDO is necessary for the development of depression in our model, the next logical question was whether serotonin depletion was ultimately responsible for the alteration in behavior. However, there was no evidence of a decrease in serotonin levels or serotonin turnover in the brain in response to inflammatory mediators. LPS resulted in an increase, not a decrease, in serotonin turnover (O'Connor et al., 2009c), and similar results have been obtained in models using Poly I:C in rats (Gibney et al., 2013). This ultimately indicates that IDO was altering behavior through another mechanism in this model. The effect of LPS on serotonin levels has not been universal, with some papers reporting a decrease in serotonin following LPS at similar time points (Ji et al., 2014; Yeh et al., 2015). These differences may be due to region of analysis, as O'Connor et al. (2009c) examined whole brain, whereas others report differences in specific regions, including the nucleus accumbens (Yeh et al., 2015) and prefrontal cortex (Ji et al., 2014). It is also possible that different strains of mice may produce different results, as strains vary in serotonin levels at baseline and in response to stress (Shanks et al., 1991).

Kynurenine Metabolites

The majority of kynurenine found in the brain during inflammation comes from the periphery (Gál and Sherman, 1980; Kita et al., 2002). It is transported into the brain via the L-type amino acid transporter, also known as solute carrier family 7. Once within the brain, kynurenine produces a variety of neuroactive metabolites, including quinolinic acid and kynurenic acid. Both quinolinic acid and kynurenic acid act at the level of the NMDA receptors, but in opposing directions. Kynurenic acid is an antagonist of the NMDA receptors (but evidence also suggest

it binds to acetylcholine nicotinic receptors) and decreases glutamate release in the brain (Birch et al., 1988). Quinolinic acid is an agonist of the NMDA receptor (Stone and Perkins, 1981), which can cause excitotoxicity and significant damage to neurons (Foster et al., 1983; Schwarcz et al., 1983; Amori et al., 2009). These 2 metabolites are produced in different cell types in the brain, with quinolinic acid primarily produced in microglia in a kynurenine monooxygenase (KMO)-dependent pathway (Espey et al., 1997) and kynurenic acid produced in astrocytes in a kynurenine aminostransferase-dependent pathway (Guidetti et al., 2007).

With our previous data demonstrating that serotonin was not depleted in our model, we hypothesized that the elevations in kynurenine metabolites could contribute to depressive-like behaviors. Indeed, LPS administration caused an elevation in quinolinic acid but not kynurenic acid in the brain as well as other KMO-dependent kynurenine metabolites (Walker et al., 2013). Blockade of quinolinic acid access to NMDA receptors by ketamine was effective at eliminating depressive-like behaviors in LPS-induced depression, but did not alter sickness behaviors or inflammation due to LPS (Walker et al., 2013). Ketamine did not alter IDO activity itself either, which suggests depressive behaviors are due to the overactivation of the NMDA receptor, which could be modulated by quinolinic acid. Walker et al. (2013) also reported elevations in another potentially harmful metabolite, 3-hydroxykynurenine (3HK). 3HK is known to be neurotoxic (Okuda et al., 1996), causes mitochondrial dysfunction (Reyes-Ocampo et al., 2015), and elevates reactive oxygen species (Shoki et al., 1998; Jeong et al., 2004). While 3HK itself may alter behavior through neurotoxic effects, it can cause substantially more damage in the presence of quinolinic acid (Guidetti and Schwarcz, 1999). So it is possible that both of these metabolites work in concert to alter neuronal functioning and change behavior.

The clinical literature also reports significant changes in kynurenine pathway metabolites in depressed patients. For example, the ratio of kynurenic acid to quinolinic acid was significantly reduced in depressed patients, and this ratio was significantly correlated with both anhedonia (Savitz et al., 2015b) and volume reductions in mood-related brain regions (Savitz et al., 2015a). In addition, patients who attempted suicide have elevated quinolinic acid levels in the CSF compared with healthy controls (Bay-Richter et al., 2014). In humans with traumatic brain injury, there is an increase in IDO and quinolinic acid in the CSF and brains of patients who had a worse recovery (Yan et al., 2015). Adding further evidence to a role for IDO and quinolinic acid in depression, the metabolites of kynurenine are elevated in depressed patients in the CSF without any corresponding change in CSF tryptophan (Raison et al., 2010). Other papers have failed to show alterations in kynurenine or its metabolites in the plasma of depressed patients (Dahl et al., 2015; Meier et al., 2015), and one reported a decrease in plasma kynurenine levels (Hennings et al., 2013). While Meier et al. (2015) did not see changes in kynurenine, they did report that depressed patients have altered kynurenic acid/quinolinic acid and kynurenic acid/3HK ratios. These differences, though, were no longer significant after controlling for sex. Upon examination of their data, they report that differences in males were driving the significant effects, suggesting that sex may be a contributing factor. Another possible explanation for the negative findings is that only a subpopulation of patients may show elevated kynurenine levels. This corresponds well with the data reporting only a portion of depressed individuals have elevated pro-inflammatory cytokines (as discussed above). Likewise, plasma kynurenine levels were increased in individuals who attempted suicide compared with healthy controls and other patients with depression (who had not attempted suicide), so severity of depression may be relevant (Sublette et al., 2011). It is important to note that kynurenine data need to be interpreted with caution, since they do not necessarily reflect ongoing low-grade inflammation. Cortisol-driven activation of the liver enzyme tryptophan 2,3 dioxygenase can also lead to marked elevations in circulating kynurenine. The best way to distinguish inflammation-driven elevations of kynurenine from other causes would be to measure the levels of neopterin, or other markers of immune activation, which is never done (Wildner et al., 2002).

It is also important to mention that mechanisms other than the kynurenine metabolites are being investigated in the inflammation-induced depression model, including brain derived neurotrophic factor (Zhang et al., 2014), leptin (Kurosawa et al., 2015), glucocorticoids (Adzic et al., 2015), and alterations in neurotransmitters, such as adrenaline/noradrenaline (Sekio and Seki et al., 2014; Zhu et al., 2015), dopamine (Yeh et al., 2015), and acetylcholine (Ming et al., 2015).

Clinical Implications: Pharmacological Targets beyond Inflammation

Inflammation is at the origin of the biological cascade that causes depressive behaviors, but it may not always be possible or reasonable to treat inflammation. By exploring downstream mechanisms, it is possible to uncover novel targets for antidepressant therapies (Figure 3). So far, a number of possible targets have been uncovered, including kynurenine metabolites and enzymes, blood-brain barrier transport mechanisms, and glutamatergic neurotransmission. Note all of these targets are working under the assumption that inflammation-induced depression is due to kynurenine metabolites, specifically quinolinic acid, that act on glutamatergic neurons in the brain.

Directly targeting kynurenine production and therefore decreasing its downstream neurotoxic metabolites is one potential avenue for treatment. The most direct method would be to prevent kynurenine accumulation by blocking IDO activity with an inhibitor of the enzyme. Currently, 3 IDO inhibitors, D1-MT, INCB024360, and GDC-0919 (formerly NLG-919), are being tested in patients with solid tumors to suppress immunotolerance of the tumor and enhance response to cancer therapy (Table 1). The specificity of action on IDO1 varies between the drugs (Li et al., 2010). INCB024360 has high specificity for IDO1 (Li Et al., 2010), while D-1MT has broader effects (for review, see Lob et al., 2009 and Moon et al., 2015). These clinical trials will give insight into the feasibility of administering IDO inhibitors in the long term, which, if successful, could be considered as possible therapeutics in specific populations of depressed patients. It may also be possible to target other enzymes, such as KMO. KMO catalyzes kynurenine into 3-HK and can be used to create quinolinic acid in microglia cells. Recently, KMO inhibitors have been proposed as potential therapeutic targets for Huntington's disease (Toledo-Sherman et al., 2015), and it may be worthwhile to explore these molecules in inflammation-induced depression. Kynurenine can alternatively produce kynurenic acid if it is metabolized by KATs instead of KMO, and because kynurenic acid has opposing roles of quinolinic acid, it could counteract its effects. Indeed, studies have demonstrated that administering nicotinylanaline will increase kynurenic acid and have a protective effect on neurons (Russi et al., 1992). Another potential mechanism to modulate the kynurenine metabolism pathway is aerobic exercise. There is already evidence of antidepressant effect of

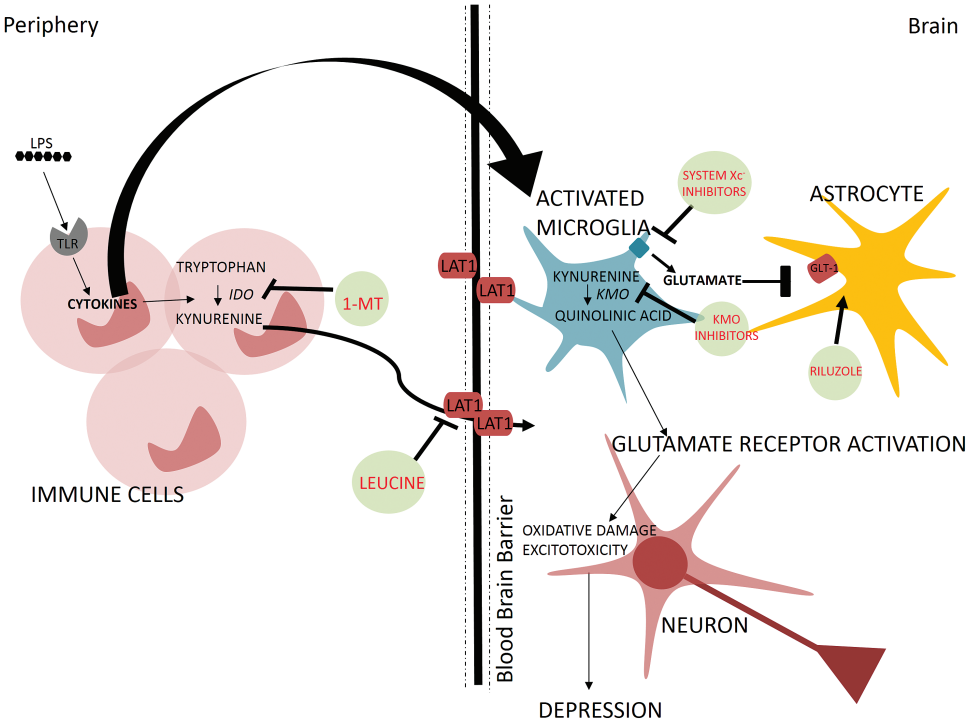

Figure 3. Possible therapeutic interventions for lipopolysaccharide (LPS)-induced model of depression. This figure demonstrates several possible therapeutic targets (green circles with red font) in our LPS-induced model of depression. One potential antidepressant route would be to block the production of kynurenine by administering inhibitors of indoleamine 2,3 dioxygenase (IDO), such as 1-methyl tryptophan. Downstream kynurenine metabolites are damaging to neurons, and therapies that inhibit their production would also be effective. For example, kynurenine 3-monoxygenase (KMO) inhibitors may be used to decrease 3-hydroxykynurenine (3-HK) or quinolinic acid production. As the majority of kynurenine in the brain is transported from the periphery, a reasonable intervention would be to prevent the transport of kynurenine. Tryptophan and kynurenine are both transported into the brain by L-type amino acid transporter. L-type amino acid transporter has a high affinity for leucine, and leucine administration could result in a decrease in kynurenine transport and thereby reduce downstream kynurenine metabolites in the brain. Lastly, upon activation microglia can release glutamate and inhibit the uptake of glutamate by astrocytes that can cause excessive glutamatergic activity. This excessive glutamatergic activity can lead to excitotoxicity or an increase in oxidative damage. Administration of inhibitors to prevent the release of glutamate from microglia would reduce glutamate receptor activation and possibly prevent depressive-like behaviors. Likewise, LPS and quinolinic acid can interfere with glutamate uptake in astrocytes. The use of riluzole has been demonstrated to increase astrocyte uptake of glutamate, and block glutamate release. GLT-1, glutamate transporter; TLR, Toll-Like Receptor.

exercise in rodents (Duman et al., 2008; Marais et al., 2009; Patki et al., 2014) and humans (Silveira et al., 2013). Overexpression of peroxisome proliferator-activated receptor-γ coactivator 1α, a protein elevated in skeletal muscle after exercise, made mice resistant to stress-induced depression by enhancing the enzymatic activity of kynurenine amino transferases and increasing production of the neuroprotective kynurenine metabolite kynurenic acid (Agudelo et al., 2014).

The majority of kynurenine in the central nervous system is transported from the periphery. This transport is mediated through L-type amino acid transporter (Fukui et al., 1991). Tryptophan, kynurenine, and other large neutral amino acids, such as leucine, compete at the transporter for entry into the brain. Recent data from our laboratory indicate that it is possible to block depressive-like behaviors following LPS injection with the amino acid l-leucine. It is hypothesized that leucine would outcompete kynurenine for transport into the brain and thus decrease central kynurenine levels. This does seem to be the case, as our preliminary findings demonstrate that there is a significant reduction in the ratio of kynurenine to tryptophan of the brain in leucine-treated rodents who were administered LPS (Walker et al., 2015). These data indicate that blood-brain transport mechanisms are a viable target for antidepressant treatment.

Excessive levels of glutamate are excitotoxic to neurons (Lucas and Newhouse, 1957), and glutamate dysfunction is a possible cause of depression (for review, see Paul and Skolnick, 2003; Sanacora et al., 2012). In both the LPS-induced and stress-based models of depression, ketamine, an NMDA antagonist, can block depressive-like behaviors (Li et al., 2011; Walker et al., 2013). Targeting glutamate activity can be done by enhancing glutamate reuptake or decreasing glutamate release by facilitating GABA or other molecules that can decrease glutamatergic activity. Astrocytes play an important role in the uptake of glutamate, which helps limit and prevent damage due to excitotoxicity. Astrocytes uptake glutamate through transporters and convert glutamate into glutamine, which can then be released back into the extracellular space and picked up by neurons. Microglia can also take up glutamate from the environment, but, importantly, upon immune activation microglia will release glutamate, which may contribute to excitotoxicity (Takaki et al., 2012; Thomas et al., 2014). A variety of factors, including LPS or TNF, can increase glutamate release from microglia (Thomas et al., 2014), and glutamate exits through two systems in microglia. The first is through the cell adhesion hemichannel (Takeuchi et al., 2006), and the other is System Xc^-, the glutamate/cysteine antiporter (Piani and Fontana, 1994; Kigerl et al., 2012). In addition, microglial release of glutamate decreases astrocytes' ability to uptake glutamate, which results in greater neuronal damage (Takaki et al., 2012). In addition, LPS alone can cause glutamate efflux from astrocytes through the release of ATP (Pascual et al., 2012). Likewise, quinolinic acid can prevent the uptake of glutamate by astrocytes through a decrease in the glutamate transporter (Tavares et al., 2002). There is an indication that both

Table 1. Clinical Trials with Drugs Targeting the Kynurenine Pathway

Drug	Target	Clinical Trial Target(s)	Clinical Trial Identifier	**Status**
D-1MT	IDO inhibitor			
(Indoximod)		Lung cancer	NCT02460367	Recruiting
		Breast cancer	NCT01792050	Recruiting
		Brain tumors	NCT02502708	Recruiting
		Solid tumors	NCT00739609	Terminated
		Melanoma	NCT02073123	Recruiting
		Malignant brain tumors	NCT02052648	Recruiting
		Pancreatic cancer	NCT02077881	Recruiting
		Breast cancer	NCT01302821	Withdrawn
		Solid tumors	NCT00567931	Completed, no results
INCB024360	IDO inhibitor			
(epacadostat)		Epithelial ovarian, fallopian tube or primary peritoneal cancer	NCT01982487	Withdrawn
		Ovarian, fallopian tube, primary peritoneal cancer in remission	NCT02166905	Recruiting
		Ovarian, fallopian tube, primary peritoneal cancer in remission	NCT01685255	Completed
		Ovarian, fallopian tube, primary peritoneal cancer	NCT02042430	Active
		Ovarian, fallopian tube, primary peritoneal cancer	NCT02118285	Recruiting
		Myelodysplastic syndromes	NCT01822691	Completed
		Platinum resistant ovarian, fallopian, peritoneal cancer	NCT02575807	Recruiting
		Metastic melanoma	NCT01604889	Active
		Advanced solid tumors	NCT02559492	Recruiting
		Advanced malignancies	NCT01195311	Completed, no results
GDC-0919	IDO Inhibitor			
		Solid tumor	NCT02471846	Recruiting
		Solid tumor	NCT02048709	Recruiting

Abbreviations: IDO, indoleamine 2,3 dioxygenase; 1-MT, 1-methyl tryptophan.

the release of glutamate from microglia and the modulation of astrocytes due to LPS can be reversed when treated with antagonists of 1 of the 2 transporters that microglia use to export glutamate (Domercq et al., 2007; Takeuchi et al., 2008). Riluzole is a drug used to treat amytrophic lateral sclerosis. It enhances the expression of glutamate transporters on astrocytes (Carbone et al., 2012), resulting in increased astrocytic glutamate uptake in rats (Frizzos et al., 2004; Yoshizumi et al., 2012), and decreases glutamate release from neurons (Wang et al., 2004). Riluzole has antidepressant effects as determined by the forced swim test (Gourley et al., 2012) and can reverse depression due to chronic stress in rodents (Banasr et al., 2010). Indeed, riluzole has been tested humans with depression with promising results (Zarate et al., 2005; Sanacora et al., 2007; Ibrahim et al., 2012; Brennan et al., 2010). This drug could be worth investigating in inflammation-induced depression. Overall, targeting the glutamate transport systems within microglia and astrocytes could be another viable method to eliminate depressive-like behaviors.

Final Remarks

Depression is a debilitating and recurring disorder that is estimated to affect nearly 20% of the population. The most common antidepressant therapies are oral medications that show variable response rates and take weeks to improve the moods of patients. The current medications therefore still have much room for improvement. While antiinflammatory agents have been tested as antidepressants, with some success in special populations of patients, targeting a more specific mechanism could have a greater response rate and be applicable to a wider range of patients. The inflammation-induced model of depression has uncovered the tryptophan-kynurenine pathway as critical for depression, and it has provided a variety of new targets for antidepressant therapies. With further analysis of these downstream pathways, it is possible to also discover mechanisms that are more broadly applicable to other models of depression.

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Statement of Interest

None.

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