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Role of the kynurenine metabolism pathway in inflammation-induced depression – Preclinical approaches

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Abstract

Physically ill patients with chronic inflammation often present with symptoms of depression. Our understanding of the pathophysiology of inflammation-associated depression has benefited from preclinical studies on the mechanisms of sickness and clinical studies on the symptoms of sickness and depression that develop in patients treated with immunotherapy. Sickness behavior develops when the immune system is activated by pathogen- or damage-associated molecular patterns. It is a normal biological response to infection and cell injury. It helps the organism to mobilize its immune and metabolic defenses to fight the danger. Depression emerges on the background of sickness when the inflammatory response is too intense and long lasting or the resolution process is deficient. The transition from sickness to depression is mediated by activation of the kynurenine metabolism pathway that leads to the formation of neurotoxic kynurenine metabolites including quinolinic acid, an agonist of N-methyl-D-aspartate receptors. The neuroimmune processes and molecular factors that have been identified in the studies of inflammation-associated depression represent potential new targets for the development of innovative therapies for the treatment of major depressive disorders.

Keywords

Inflammation; Sickness; Depression; Indoleamine 2,3-dioxygenase; Kynurenine; Quinolinic acid; NMDA receptor; Brain; Microglia; Cytokines; Behavior

History of a discovery: From inflammation-induced sickness to depression

I read with intense excitement the original research article by Munn and colleagues on the prevention of allogeneic fetal rejection by tryptophan catabolism when it came out in *Science* in 1998 (Munn et al. 1998). This landmark paper provided a very simple explanation for what had puzzled reproductive immunologists for a long time: how the foreign mammalian conceptus can avoid immune attack and defend itself against rejection by the mother's immune system. Munn and colleagues showed convincingly that maternal T-cell tolerance to the fetal allografts can develop because the maternal immune response to

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the allogeneic conceptus activates the tryptophan-metabolizing enzyme indoleamine 2,3 dioxygenase (IDO1) in the trophoblast at the level of the maternal–fetal interface. IDO1 metabolizes tryptophan, an amino acid nutrient essential for T-cell proliferation and cytotoxicity, into kynurenine. The resulting depletion of tryptophan leads to T-cell anergy.

I had no special interest in reproductive immunology; my excitement came from the realization that a process similar to the one described by Munn and colleagues could occur in the brains of inflamed organisms and be responsible for some of the effects of cytokines on the brain. We had already demonstrated that systemic inflammation induces the production of proinflammatory cytokines in the brain and that these proinflammatory cytokines cause sickness behavior (Dantzer 2001). If proinflammatory cytokines could activate IDO at the maternal–fetal interface, they could certainly do it in the brain. The result would be a decrease in the bioavailability of tryptophan for the synthesis of serotonin, which could account for why inflammation is associated not only with sickness behavior but also with major depressive disorders.

It took us some time and effort to test this hypothesis. Thanks to a collaboration with Maes, who was then at the University of Maastricht in the Netherlands, we already had evidence that circulating levels of tryptophan were decreased in cancer patients treated with interleukin (IL)-2 or interferon (IFN)- α (Capuron et al. 2002b). What was striking in these findings was that the severity of symptoms of depression was positively correlated with the magnitude of the decrease in tryptophan concentrations during the treatment. However, in order to test the hypothesis that activation of IDO is responsible for the development of inflammation-induced depression, we first had to show in mice that systemic activation of the immune system activates IDO in the brain and then that the time course of this response is compatible with the time course of the development of symptoms of depression.

There were several hurdles to jump over before this demonstration could be achieved. First, most of our work on the brain effects of cytokines had been done in rats. However, IDO activation in microglia and astrocytes in response to systemic or central inflammation was already known to be minimal in the rat (Heyes et al. 1997), probably because this species responds to systemic inflammation by a strong induction of nitric oxide synthase, with the resulting nitric oxide opposing IDO activation (Thomas et al. 1994). We therefore had to switch to a mouse model (Heyes et al. 1997). Second, we had to take into account the fact that the bioassays for assessing depression in rodents were based on behavioral responses that are very sensitive to sickness. The reduction in sucrose preference that is commonly used to assess anhedonia was going to be biased by the decreased appetite present in sick animals. In the same manner, the increased duration of immobility in the forced-swim and tail-suspension tests, which are used to assess helplessness, was going to be difficult to separate from the decreased motor performance associated with sickness. In other words, there was no way for us to convince reviewers that we could measure depression-like behavior independently of sickness behavior in inflamed mice.

One possibility to circumvent this issue was to wait until sickness dissipated before measuring depression-like behavior. This turned out to be the right strategy, as our time-course studies of IDO activation in the brain revealed that IDO enzymatic activity requires

24 h to develop in the brains of mice injected with lipopolysaccharide (LPS) or superantigen at the periphery (Lestage et al. 2002) (Fig. 1). By that time, sickness behavior measured by reduced food intake, decreased social exploration, and reduced locomotor activity would have fully dissipated and could therefore no longer account for the increased duration of immobility in the forced-swim test and the reduced sucrose preference presented by LPS-treated mice (Frenois et al. 2007). This dissociation between sickness behavior and depression in response to LPS fitted very well with the already-demonstrated temporal dissociation between the neurovegetative symptoms and the cognitive/affective symptoms of depression seen in patients treated with IFN- α (Capuron et al. 2002a) (Fig. 2).

The only methodological problem left was the relatively short duration of LPS-induced depression, which did not last for more than a few hours. We therefore needed to set up a model of chronic inflammation-induced depression. Because the main driver of IDO activation is IFN- γ , we selected an IFN- γ -inducer pathogen represented by *Bacillus Calmette-Guerin* (BCG), an attenuated form of *Mycobacterium bovis*, to activate IDO chronically. We confirmed that mice inoculated with BCG had chronically elevated IDO activity in the lung and brain (Moreau et al. 2005). We were also able to demonstrate that the initial episode of sickness that developed a few days after BCG inoculation was followed by long-lasting decrease in sucrose preference and increase in immobility in the forced-swim and tail-suspension tests (Moreau et al. 2008).

On the basis of these results, we were able to move to the next step in this research and demonstrate that IDO activation is crucial for the transition from sickness behavior to depression-like behavior in both LPS-treated and BCG-treated mice (O'Connor et al. 2009a; O'Connor et al. 2009b; O'Connor et al. 2009c). This allowed us to investigate the mechanism responsible for inducing depression downstream of IDO. This chapter will show how the immune-mediated tryptophan depletion hypothesis of inflammation-induced depression has been ultimately replaced by the kynurenine metabolism hypothesis, and will discuss how this mechanism can be targeted for treating inflammation-induced depression.

From tryptophan starvation to neurotoxic kynurenine metabolites

Most of the tryptophan we ingest is metabolized along the kynurenine pathway, and only a tiny amount since 1%, is converted into serotonin (Fig. 3). The conversion of tryptophan into N-formyl kynurenine is catalyzed by the liver enzyme tryptophan 2,3 dioxygenase (TDO), also known as tryptophan pyrrolase. IDO is the product of the *ido1* gene and is sometimes labeled as IDO1. Another IDO-like enzyme was recently discovered. It is the product of a different gene, known as *ido2*, that is situated on the same chromosome as *ido1* and that probably emerged through gene duplication. This enzyme was accordingly labeled as IDO2. It also has the ability to metabolize tryptophan, although its enzymatic activity is much lower than that of IDO1. Its physiological and pathophysiological roles are still unclear (Fatokun et al. 2013). In this chapter we will refer only to IDO1, which we will continue to label as "IDO".

IDO was first purified from the rabbit intestine and found to have a broader substrate specificity than did TDO (Takikawa 2005). Yoshida and Hayaishi from the Department of

Medical Chemistry at the Faculty of Medicine in Kyoto were the first researchers to show that LPS injected intraperitoneally induces IDO in the lungs, peaking 24 h after injection (Yoshida and Hayaishi 1978). The same effect was obtained after viral infection (Yoshida et al. 1979). IFN- γ mimics the effect of LPS and viral infection on induction of IDO, and cloning of the *ido1* gene confirmed the ability of IFN- γ to upregulate IDO (Taylor and Feng 1991). IFN- γ and other cytokines increase the transcriptional activation of *ido1*. More specifically, IFN- γ -induced signal transducer and activator of transcription 1 α (Stat1) activates *ido1* gene expression by binding to γ -activated sequences in the *ido1* regulatory region. In addition, IFN- γ induces IFN regulatory factor-1, which binds to IFN- γ -stimulated response elements (ISRE) in the *ido1* regulatory region. Tumor necrosis factor (TNF)- α synergistically increases the transcriptional activity of *ido1* in response to IFN- γ by increasing Stat1 and ISRE (Robinson et al. 2006).

Activation of IDO leads to enhanced metabolism of tryptophan into kynurenine, which decreases the bioavailability of tryptophan for its metabolic functions. IDO-induced tryptophan starvation has long been believed to be responsible for the metabolic control of immune responses (Munn and Mellor 2013) (Fig. 4). Tryptophan starvation that develops in the inflammatory microenvironment triggers amino-acid-sensing pathways and in particular the serine/threonine protein kinase general control nonderepressible 2. This leads to enhanced generation of Foxp3⁺ regulatory T cells and inhibition of T effector cells. Tryptophan starvation also inhibits mechanistic target of rapamycin (mTOR) activity, leading to the same results.

The importance of tryptophan starvation in the biological consequences of IDO activation has recently been questioned. Tryptophan remains available in the extracellular milieu and in the blood in relatively high concentrations during IDO activation, and most cells are able to incorporate tryptophan with high efficiency even in conditions of low tryptophan availability. The attention has therefore shifted to the possible activity of kynurenine generated from tryptophan by IDO and the kynurenine metabolites generated by further enzymatic reactions (Fig. 3).

In contrast to what was initially believed, kynurenine is not biologically inactive. It acts as a high-affinity ligand of the aryl hydrocarbon receptor (AHR). AHR is present in many different cells and plays an important protective role at the level of mucosal and barrier tissues (Cella and Colonna 2015). Activation of AHR by kynurenine has immunosuppressive properties on innate and adaptive immunity. Binding of kynurenine to AHR downregulates inflammatory responses mediated by LPS acting on macrophages and promotes endotoxin tolerance (Kimura et al. 2009; Bessede et al. 2014). In the presence of transforming growth factor- β , kynurenine reduces the differentiation of T cells into highly inflammatory Th17 cells and promotes the generation of Foxp3⁺ regulatory T cells (Mezrich et al. 2010). In addition to its biological activity, kynurenine is metabolized into kynurenine metabolites by additional enzymatic reactions. In particular, kynurenine is converted by kynurenine aminotransferases into kynurenic acid and by kynurenine mono-oxygenase and other enzymes into 3-hydroxy kynurenine, 3-hydroxyanthralinic acid, and quinolinic acid (Fig. 3). These last kynurenine metabolites have additive cytotoxic effects on T lymphocytes (Terness et al. 2002).

Two independent lines of research have dominated the studies on tryptophan and tryptophan metabolism in the central nervous system. The first line of research finds its origin in the early 1970s and focuses on the role of tryptophan in the synthesis of serotonin (Lehnert and Wurtman 1993). The second line of research focuses on the physiology and pathophysiology of kynurenine and its metabolites in the brain (Schwarcz et al. 2012). Concerning the first line of research, two nutritionists from Massachusetts Institute of Technology, Fernstrom and Wurtman, reported that it was possible to modify brain concentrations of serotonin in rats by administering L-tryptophan at the periphery (Fernstrom and Wurtman 1971). This modification was possible with as little as 12.5 mg/kg tryptophan, which is much less than the amount of tryptophan rats normally consume daily in dietary protein. Because of this, Fernstrom and Wurtman proposed that physiological fluctuations in plasma tryptophan concentrations influence brain serotonin levels. Given the observation that tryptophan hydroxylase is not normally saturated by the physiological concentrations of its substrate, it was theoretically possible to increase brain serotonin by administering its precursor at the periphery and ultimately to treat disease states related to reduced brain serotonin (Fernstrom 1981). Curzon at the London Institute of Neurology proposed a link between major depressive disorders and enhanced degradation of tryptophan along the kynurenine metabolism pathway because of an increased activity of TDO in response to elevated endogenous cortisol levels (Curzon 1969; Curzon and Bridges 1970).

Despite all these favorable elements, tryptophan supplementation in humans never held to its promises. Ingestion of tryptophan did not improve mood and at best induced some increase in drowsiness—but only after severe initial nausea and headache (Greenwood et al. 1975). Other studies using tryptophan supplementation indicated that increased serotonin decreased quarrelsomeness and increased agreeableness in social interactions, therefore acting on mood in a very indirect manner (Young 2013). In contrast, acute tryptophan depletion produced by ingestion of a mixture of branched-chain amino acids other than tryptophan that competed with tryptophan for transport into the brain turned out to be an easy way to decrease brain serotonin levels momentarily and lower mood. However, this effect occurred reliably only in subjects with a personal or a family history of depression (Young 2013; Ruhe et al. 2007).

It is not surprising that the initial hypothesis for the relationship between inflammation and depression focused on decreased serotonergic neurotransmission. By decreasing circulating levels of tryptophan, inflammation-induced IDO activation has the potential of mimicking the effect of acute tryptophan depletion on serotonin metabolism. In addition, IFN- γ induces guanosine triphosphate cyclohydrolase I (GTP-CH) in macrophages. GTP-CH is a key factor in the synthesis of biopteridines. Activation of GTP-CH favors the formation of neopterin over that of tetrahydrobiopterin (BH4). BH4 is an important co-factor for the enzymatic activity of tryptophan hydroxylase, which metabolizes tryptophan into 5-hydroxy tryptophan, an essential step in the synthesis of serotonin. However, as mentioned in the first section of this chapter, there is no evidence for decreased brain tryptophan and serotonin levels in inflammation-associated depression. Much of the speculation on GTP-CH has switched to its role in the enzymatic activity of tyrosine hydroxylase and the formation of phenylalanine, a precursor of dopamine (see the chapter by Fuchs et al. in this volume).

In parallel with the diminution of the tryptophan starvation hypothesis in immunology, studies on the mechanisms of inflammation-associated depression began to examine the kynurenine metabolism hypothesis, making use of what was already known about the pharmacology of kynurenines in the central nervous system. Lapin at the Bekhterev Psychoneurological Institute in Leningrad, USSR, had observed that kynurenine and its metabolites (mainly 3-hydroxy anthranillic acid, anthranillic acid, picolinic acid, and nicotinic acid) had anti-serotonin and anti-tryptamine activities (Lapin 1972). When injected into the brain ventricles of mice, kynurenine, quinolinic acid, 3-hydroxy anthranillic acid, xanthurenic acid, picolinic acid, and nicotinic acid had potent pharmacological activities manifested by increased motor activity and convulsions (Lapin 1978). Kynurenic acid was found to be able to antagonize the convulsant effect of kynurenine and quinolinic acid (Lapin 1983).

Research on the pharmacology and physiology of brain kynurenines has made great progress since these initial studies (Schwarcz et al. 2012). Kynurenic acid is a broad spectrum competitive antagonist of glutamate receptors and an inhibitor of the $\alpha 7$ nicotinic acetylcholine receptor. Quinolinic acid acts as an agonist of N-methyl-D-aspartate (NMDA) receptors, mainly in the forebrain. Other metabolites of kynurenine, including 3-hydroxy kynurenine, 3-hydroxy anthranilic acid, and anthranilic acid, have no direct effect on neuronal activity but participate in complex pro-oxidative and anti-oxidative processes. However, most of the studies on the physiology and pharmacology of kynurenine metabolites completely ignored the role of immune-mediated IDO activation and focused primarily on the neuronal effects of these metabolites.

Inflammation-induced depression and glutamate neurotransmission

The possibility of a cellular compartmentalization of kynurenine metabolism emerged when *in vitro* studies on primary cultures of astrocytes and microglia stimulated by IFN- γ showed that kynurenic acid is produced mainly by astrocytes whereas quinolinic acid is only produced by microglia (Guillemin et al. 2005). Since kynurenic acid acts as an antagonist whereas quinolinic acid acts as an agonist of NMDA receptors, Müller, Myint, and Schwarz from the Department of Psychiatry at the University of Munich, proposed that inflammation driven by Th1 cytokines such as IFN- γ shifts the equilibrium between these two opposite poles toward neurotoxicity by promoting microglial activation and downregulating astrocyte activity. Major depressive disorders would be the result of this shift. Conversely, Th2 cytokines such as IL-4 and IL-10 oppose the production and release of Th1 cytokines and therefore downregulate IDO. In association with astrocyte activation, this would result in an overproduction of kynurenic acid that would be responsible for schizophrenia (Muller et al. 2009).

A possible role for IDO activation in the pathophysiology of major depressive disorders was first hypothesized on the basis of the correlation between the fall in plasma levels of tryptophan and the intensity of depressive symptoms in cancer patients treated with IFN- α and/or IL-2 (Capuron et al. 2002b). Preclinical studies carried out in mice injected with LPS or inoculated with BCG confirmed that pharmacological or genetic blockade of IDO activation abrogated the development of depression-like behavior without interfering with

signs of sickness behavior (O'Connor et al. 2009b; O'Connor et al. 2009c). These findings were interpreted to suggest that IDO activation functions as a molecular switch favoring the emergence of depression on a background of sickness (Dantzer et al. 2008). However, further investigation into the metabolism of tryptophan in inflammation-induced depression could not reveal any evidence of tryptophan starvation in response to inflammation. Tryptophan levels in the brain remained constant or even increased in response to inflammation, despite the reduction in circulating tryptophan levels. Furthermore, detailed analysis of kynurenine metabolites based on tandem mass spectroscopy of the brains of LPS-treated mice revealed an activation of the kynurenine amino transferase branch of kynurenine metabolism leading to 3-hydroxy kynurenic acid and quinolinic acid, without any change in the kynurenine aminotransferase branch leading to kynurenic acid (Walker et al. 2013). These results essentially confirmed the hypothesis formulated by Müller and colleagues.

Because quinolinic acid acts as an agonist of the NMDA receptor, the next step was to test whether blockage of NMDA receptors abrogates inflammation-induced depression. Ketamine was selected for this purpose. However, ketamine has anti-inflammatory properties. It was therefore important to administer this compound at a time at which the inflammatory cascade triggered by inflammation had already developed and IDO was fully activated. This was done by administering ketamine immediately before the behavioral tests of depression-like behavior in mice treated 24 h earlier with LPS. As expected, this treatment abrogated the development of depression-like behavior in LPS-treated mice (Walker et al. 2013). The confirmation that this effect was due to blockage of NMDA receptors rather than to another uncontrolled effect of ketamine was verified by injecting mice treated with LPS and ketamine with the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline-2,3-dione in order to block enhanced AMPA receptor glutamatergic neurotransmission due to NMDA receptor blockade. As expected, this treatment restored the LPS-induced depressive like behavior that had been blocked by ketamine. Whether quinolinic acid alone is sufficient to induce depression-like behavior or whether it needs to synergize with increased extracellular glutamate is discussed in the section on transport mechanisms below (see also (Dantzer and Walker 2014)).

Transport mechanisms regulating the communication between peripheral and central kynurenine pathways

Transport mechanisms regulate the communication between peripheral and central kynurenine pathways under normal and inflammatory conditions (Schwarcz et al. 2012). Experiments carried out in pentobarbital-anesthetized rats using the *in situ* brain perfusion technique showed that kynurenine and 3-hydroxykynurenine are transported into the brain along a concentration gradient by the large amino acid transporter LAT1, which also transports tryptophan and other branched-chain amino acids into the brain (Fukui et al. 1991). Among the other metabolites, only anthralinic acid enters the brain in sizeable quantities, but by passive diffusion. Although kynurenine can be formed in the brain by IDO present in microglial cells and brain macrophages, most of the brain kynurenine – 78% in

gerbils – originates from the periphery (Kita et al. 2002). In response to systemic immune activation caused by intraperitoneal injection of LPS, this percentage goes up to 100% despite the fact that IDO activity increases in the brain as well as in the periphery (Lestage et al. 2002). In this condition, brain quinolinic acid is formed mainly from blood kynurenine (52%) and blood quinolinic acid (40%), meaning that the permeability of the blood–brain barrier to kynurenine must increase (Kita et al. 2002). When the inflammation is central rather than peripheral in origin, the brain production of kynurenine and quinolinic acid takes over and is responsible for more than 98% of the total brain levels of kynurenine and quinolinic acid (Kita et al. 2002).

LAT1 is a heterodimeric membrane transport protein that is composed of a heavy subunit protein 4F2hc/CD98 coded by the *SLC3A2* gene and a CD98 light subunit protein encoded by the *SLC7A5* gene. This sodium-independent transporter is abundant at the level of the blood–brain barrier, where it controls the influx of large neutral amino acids in the brain. It is also found in astrocytes, in which it probably controls the influx of kynurenine that is further metabolized into kynurenic acid (Speciale et al. 1989). Because LAT1 transports large neutral amino acids, such as leucine, phenylalanine, and tryptophan, it is theoretically possible to compete with the entry of kynurenine into the brain by increasing the concentrations of these competing amino acids at the periphery. Proof of principle for this possibility was recently obtained *in vitro* using cortical slices of rat brain incubated with kynurenine and competing amino acids for LAT1. Leucine and other branched-chain amino acids inhibited the uptake of kynurenine by brain slices (Sekine et al. 2015).

Another transporter of importance for the relationship between inflammation and depression is system x_c^- . This system functions as an antiporter in the sense that it exchanges extracellular L-cystine for intracellular L-glutamate (Bridges et al. 2012). Like LAT1, x_c^- is a heterodimeric amino acid transporter composed of a heavy chain 4F2HC and a light chain xCT or SLC7A11. The intracellular transport of cysteine is an essential step for the synthesis of glutathione, making system x_c^- an important player in intracellular redox processes. System x_c^- is upregulated in activated microglia, probably because of the necessity of these cells to protect themselves from the oxidative stress they are submitted to while producing inflammatory mediators. This is associated with an increased release of glutamate formed from glutamine via an enzymatic reaction catalyzed by glutaminase. LPS co-injected with cystine into the spinal cord gray matter induces glutamate-dependent neurotoxic inflammation (Kigerl et al. 2012). Another mechanism by which inflammation can increase extracellular glutamate is by impairing astrocytic glutamate uptake (Tilleux and Hermans 2007). In either case, excessive extracellular glutamate induces excitotoxicity by activating AMPA receptors. This effect could synergize with the NMDA-dependent effect of quinolinic acid to promote the development of depression.

IDO activation and behavioral alterations in other animal models of inflammation

There is accumulating evidence of a role for IDO activation in the behavioral alterations that develop in animal models of exposure to various immune and non-immune insults.

Human immunodeficiency virus (HIV) infection is accompanied by a high rate of comorbid clinical depression. Intracerebroventricular administration of the HIV transactivator of transcription (Tat) protein induced depression-like behavior in mice, measured by increased immobility in the forced-swim test and decreased sucrose preference (Lawson et al. 2011). These behavioral alterations were associated with increased expression of IDO in the brain. Experiments with murine organotypic hippocampal slices confirmed that HIV Tat increased expression of IDO and showed that this effect was mediated by the p38 mitogen-activated protein kinase (Fu et al. 2011). Viral infection can be mimicked by injection of polyinosinic:polycytidylic acid (poly I:C). Poly I:C is structurally similar to double-stranded RNA and differs from LPS by activating Toll-like receptor (TLR)3 instead of TLR4. Systemic administration of poly I:C to rats induced behavioral signs of anxiety and depression associated with increased expression of IDO in the frontal cortex and hippocampus up to 48 h after treatment (Gibney et al. 2013). Pneumococcal meningitis was associated with long-term changes in motor activity and cognitive deficits in recovered mice (Too et al. 2014). Motor activity was no longer altered in IDO knockout mice, but cognitive deficits were still present.

Autoimmune disorders are also frequently associated with clinical depression, but the role of IDO in this association has not been studied in a systematic manner. In a murine model of lupus, the development of depression-like behavior was associated with increased levels of kynurenine pathway metabolites, but the causality was not tested (Li et al. 2015b). Similar effects were observed in response to CD40 ligand–CD40 immune activation, a murine model of autoimmune disorders. Despite evidence for increased plasma and brain levels of kynurenine and its metabolites, chronic administration of a selective IDO inhibitor had no effect on sickness behavior or decreased saccharin drinking, in contrast to what was observed after blockade of TNF- α action (Cathomas et al. 2015).

The observation that systemic infection in the elderly is often associated with an increased frequency of behavioral and cognitive complications is in agreement with the hypothesis of a chronic low-grade inflammation in aged subjects, the so-called inflammaging condition (Franceschi et al. 2000). Aged mice responded to LPS by an enhanced induction of peripheral and brain IDO and an increased duration of depression-like behavior (Godbout et al. 2008). The increase in brain IDO expression was present in microglia isolated from aged mice (Henry et al. 2009). Similar findings were observed in mice inoculated with BCG (Kelley et al. 2013).

Because of the frequent co-occurrence of chronic pain and depression, the possibility that these two conditions share a common biological mechanism represented by inflammation-induced IDO activation was investigated in a rat model of inflammatory arthritis induced by intra-articular injection of complete Freund adjuvant (Kim et al. 2012). This treatment increased IDO enzymatic activity in the hippocampus via an IL-6–dependent mechanism. Administration of the IDO inhibitor 1-methyl-tryptophan at the periphery or in the hippocampus abrogated both mechanical allodynia and increased immobility time in the forced-swim test in arthritic rats. In the same manner, IDO1 knockout mice did not develop hyperalgesia and increased immobility in the forced-swim test in response to intra-articular injection of complete Freund adjuvant, in contrast to wild type mice. These results were

interpreted to indicate that brain IDO activity regulates both chronic pain and depression. However, the generality of this interpretation is questionable, as we could not demonstrate any role for IDO activation in chronic pain in a mouse model of peripheral neuropathy induced by spared nerve injury, despite a clear role for IDO in the depression-like behavior displayed by mice in response to spared nerve injury. In this last experiment, IDO activation was only observed at the periphery, not in the brain, and the depression-like behavior was caused by the increased formation of quinolinic acid as a result of the activation of the kynurenine monooxygenase branch of kynurenine metabolism in the hippocampus contralateral to the site of nerve injury (Zhou et al. 2015).

Exposure to various stressors can activate the kynurenine metabolism pathway. However, whether this is due to immune-dependent IDO activation or to corticosterone-induced TDO activation is not always clear. Mice exposed to a model of unpredictable chronic mild stress to induce depressive-like behavior showed increased kynurenine metabolism both at the periphery and in the brain (Laugeray et al. 2010). Maternal separation, which induces long-lasting behavioral alterations in mice, had the same effect (Gracia-Rubio et al. 2016). Inescapable exposure of mice to a rat predator had also long-lasting effects on behavior and kynurenine metabolism in the brain (Miura et al. 2011). The role of TDO was assessed in the development of increased immobility in the forced-swim test in rats submitted to chronic restraint for 2 h per day. Inhibition of TDO by allopurinol abrogated the chronic stress-related increase in immobility and the accompanying increase in circulating kynurenine levels (Gibney et al. 2014).

Various forms of brain injury can activate IDO. Cerebral ischemia–reperfusion in mice enhanced IDO activity as measured by increases in the plasma ratio of kynurenine to tryptophan and IDO expression in cerebral arterioles (Jackman et al. 2011). However, blockade of IDO activation by 1-methyl tryptophan or genetic deletion of *ido1* did not affect overall outcomes as measured by neurological function and total brain infarct volume and swelling. Whether IDO activation plays a role in the etiology of post-stroke depression has not yet been tested (Spalletta et al. 2006). In a rat model of chronic temporal lobe epilepsy induced by a combination of lithium chloride and pilocarpine, blockade of IDO activation by the anti-inflammatory tetracycline derivative minocycline or the IDO antagonist 1-methyl tryptophan abrogated epilepsy-associated depression-like behavior measured by decreased sucrose preference and increased immobility in the forced-swim test (Xie et al. 2014). However, blockade of IDO activation had no effect on spontaneous seizures.

Targeting inflammation-induced depression: translational aspects

The demonstration of a causal relationship between inflammation-induced activation of IDO and the kynurenine metabolism pathway on one hand and depression on the other hand opens a number of opportunities for treatment of inflammation-induced depression. Fig. 5 represents the different steps of the process leading from inflammation to depression. Administration of anti-inflammatory drugs represents an obvious option. However, all of the attempts to treat depression by targeting inflammation have been made by administering the anti-inflammatory compound preventively. Several instances of this type of study have been mentioned in the previous sections of this chapter. In general, minocycline and cytokine

antagonists are effective to block inflammation-induced depression when administered before immune stimulation. The same effect is obtained with a wide variety of anti-inflammatory or anti-oxidant natural compounds, such as curcumin, apigenine, honkiol, xiaobuxin-tang flavonoid extract, perillaldehyde, ginseng saponins, and alpha-tocopherol (Wang et al. 2014; Li et al. 2015a; Sulakhiya et al. 2014; An et al. 2015; Ji et al. 2014; Kang et al. 2011; Manosso et al. 2013). However, it is not known whether the anti-inflammatory treatment can block behavioral signs of depression once they have developed.

Classical antidepressants have been shown to have anti-inflammatory properties that vary depending on the drug, the treatment schedule, and the type of assay (Walker 2013). An optimum strategy to treat inflammation-associated depression would then be to select the antidepressant that combines anti-inflammatory and anti-depressant properties. However, it is difficult to classify antidepressants on the basis of their anti-inflammatory properties because the data that are available in the literature are often contradictory. In addition, there has been no attempt to relate at the preclinical level their anti-inflammatory activity with their ability to decrease depression-like behavior. Most studies have been carried out with the specific serotonin reuptake inhibitor fluoxetine. Fluoxetine was able to abrogate depression-like behavior induced by the parasite *Trypanozoma cruzi* in mice (Vilar-Pereira et al. 2012). Although the parasitic disease was associated with IDO activation, there was no indication that fluoxetine acted by blocking IDO activation. Fluoxetine was also able to abrogate depression-like behavior induced by systemic TNF- α in mice, but once more there was no indication that this was due to the anti-inflammatory effect, if any, of fluoxetine (Kaster et al. 2012). The only study in which this aspect was considered yielded negative results: chronic administration of fluoxetine blocked the increased immobility displayed by tumor-bearing mice in the forced-swim test, but this effect was not associated with any alteration in expression of hippocampal proinflammatory cytokines and kynurenine mono-oxygenase (Norden et al. 2015a). In contrast, ibuprofen attenuated both depression-like behavior and hippocampal proinflammatory cytokine expression (Norden et al. 2015b). It is important to note that all forms of inflammation-induced depression are not sensitive to fluoxetine treatment. BCG-induced depression-like behavior was actually resistant to acute administration of fluoxetine and escitalopram but sensitive to acute administration of the tricyclic antidepressant imipramine, the dual serotonin/norepinephrine reuptake inhibitor duloxetine, and the dual dopamine/norepinephrine reuptake inhibitor nomifensine (Vijaya Kumar et al. 2014).

IDO activation is the molecular switch that favors the transition from sickness to depression; thus, it should be possible to treat inflammation-induced depression by blocking IDO. Although this works well in experimental studies of inflammation-induced depression, there are several obstacles to this strategy, represented by the lack of approved IDO antagonists, the possible side effects of IDO antagonists on the immune system and in particular the increased risk of autoimmune disorders, and the lack of data on the ability of IDO antagonism to reverse signs of depression when used for cure rather than for prevention.

Because most of the kynurenine that is found in the brain during systemic inflammation comes from the periphery, it should be possible to target the transport mechanisms that control kynurenine influx into the brain to prevent the formation of neurotoxic kynurenine

metabolites. The administration of branched-chain amino acids competing with kynurenine for transport via LAT1 represents a theoretically viable solution, providing this does not at the same time limit the brain influx of tryptophan. L-leucine is a good candidate for this strategy because it simultaneously upregulates LAT1, decreases the production of proinflammatory cytokines, and activates mTOR in the brain, which could favor synaptic plasticity (De Bandt and Cynober 2006; Rosario et al. 2013; Fromentin et al. 2012). We have obtained encouraging preliminary results in LPS-treated mice administered L-leucine. Systemic administration of this amino acid before and 6 h after LPS abrogated depression-like behavior measured 24 after LPS. This effect was associated with a decrease in brain kynurenine levels but no change in brain tryptophan levels (Walker et al. 2015).

Other ways of interfering with the formation of neurotoxic kynurenine metabolites include blocking kynurenine mono-oxygenase or favoring the kynurenic acid branch of kynurenine metabolism. Inhibition of kynurenine mono-oxygenase blocked the depression-like behavior developed by mice submitted to spared nerve injury (Zhou et al. 2015). In the same manner, both kynurenine mono-oxygenase-deficient mice and IDO-deficient mice were protected from inflammation-induced deficits in novel-object recognition (Heisler and O'Connor 2015). Kynurenine monooxygenase inhibition not only inhibits the formation of 3-hydroxy kynurenine and quinolinic acid, but also increases the brain concentrations of the neuroprotective metabolite kynurenic acid. This strategy has therefore been proposed to ameliorate the neurodegeneration that develops in a mouse model of Huntington disease (Zwilling et al. 2011). However, the specificity of the drug used to block kynurenine monooxygenase has been questioned (Beconi et al. 2012).

Convergence of neurotoxic kynurenine metabolites and excess extracellular glutamate on glutamatergic neurotransmission makes NMDA receptor a potential target for treatment of inflammation-associated depression. As mentioned earlier in this chapter, preventive or curative administration of the noncompetitive NMDA receptor antagonist ketamine abrogated LPS-induced inflammation (Walker et al. 2013). Ketamine has some anti-inflammatory properties (Ward et al. 2011; Zhu et al. 2015), but they did not account for the antidepressant effect observed in LPS-treated mice (Walker et al. 2013). The clinical use of ketamine is limited by its psychotomimetic properties. The current development of NMDA receptor antagonists lacking these negative side effects will certainly provide new antidepressant compounds, the ability of which to treat inflammation-associated depression will still have to be determined.

Conclusion

Diagnostic criteria for major depressive disorder and depressive episodes carefully eliminate depressed mood associated with medical illness. However, depressed patients are rarely free of other medical complications. Psychiatrists commonly encounter in their clinical practice patients with major depressive disorders who have chronic coexistent medical conditions, including chronic inflammation disorders. Studies of the relationship between inflammation and depression have shed some light on the reasons for this comorbidity. Depression does not emerge out of nothingness. In the same way that anxiety disorders derive from alterations in the fear motivational system involved in the processing of real and potential

threats and the organization of subjective, behavioral, and physiological responses to these threats, depressive disorders emerge from alterations in the sickness motivational system that is responsible for reorganizing priorities in an organism at the juncture of life and death because of an ongoing infectious process. It has been possible to understand how sickness transitions into depression because the preclinical investigations at the origin of this research have carefully built on what has been learned in the clinic, in inflamed patients who develop clinical symptoms of depression. Psychobiologists have walked hand in hand with clinical psychologists and psychiatrists to design animal models of inflammation-induced depression and elaborate testable hypotheses on its pathophysiology. This research has resulted in the appearance of a number of new players on the stage of biological psychiatry, from inflammatory molecules to transport mechanisms regulating the communication between peripheral and central kynurenine metabolites.

It is possible that this adventure into inflammation-associated depression will mainstream research in biological psychiatry on a final common pathway for both immune and non-immune factors in depression, represented, for instance, by alterations in NMDA receptor activation. Even if this is the case, the inflammation detour will not have been vain since it will have allowed researchers to demonstrate unequivocally that depression is not just a disease of the neuron. It is now clear that depression is a disease of the communication between endothelial cells, glia, and neurons, and this communication is profoundly dependent on systemic factors, including inflammation.

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References

- An L, Li J, Yu ST, Xue R, Yu NJ, Chen HX, Zhang LM, Zhao N, Li YF, Zhang YZ (2015) Effects of the total flavonoid extract of Xiaobuxin-Tang on depression-like behavior induced by lipopolysaccharide and proinflammatory cytokine levels in mice. *Journal of ethnopharmacology* 163:83–87. doi:10.1016/j.jep.2015.01.022 [PubMed: 25625350]
- Beconi MG, Yates D, Lyons K, Matthews K, Clifton S, Mead T, Prime M, Winkler D, O'Connell C, Walter D, Toledo-Sherman L, Munoz-Sanjuan I, Dominguez C (2012) Metabolism and pharmacokinetics of JM6 in mice: JM6 is not a prodrug for Ro-61–8048. *Drug metabolism and disposition: the biological fate of chemicals* 40 (12):2297–2306. doi:10.1124/dmd.112.046532 [PubMed: 22942319]
- Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Biciato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazio MA, Piobbico D, Zelante T, Funakoshi H, Nakamura T, Gilot D, Denison MS, Guillemin GJ, DuHadaway JB, Prendergast GC, Metz R, Geffard M, Boon L, Pirro M, Iorio A, Veyret B, Romani L, Grohmann U, Fallarino F, Puccetti P (2014) Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature* 511 (7508):184–190. doi:10.1038/nature13323 [PubMed: 24930766]

- Bridges RJ, Natale NR, Patel SA (2012) System xc(−) cystine/glutamate antiporter: an update on molecular pharmacology and roles within the CNS. *British journal of pharmacology* 165 (1):20–34. doi:10.1111/j.1476-5381.2011.01480.x [PubMed: 21564084]
- Capuron L, Gummnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH (2002a) Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 26 (5):643–652. doi:10.1016/S0893-133X(01)00407-9 [PubMed: 11927189]
- Capuron L, Miller AH (2011) Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & therapeutics* 130 (2):226–238. doi:10.1016/j.pharmthera.2011.01.014 [PubMed: 21334376]
- Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R (2002b) Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Molecular psychiatry* 7 (5):468–473. doi:10.1038/sj.mp.4000995 [PubMed: 12082564]
- Cathomas F, Fuertig R, Sigrist H, Newman GN, Hoop V, Bizzozzero M, Mueller A, Luippold A, Ceci A, Hengerer B, Seifritz E, Fontana A, Pryce CR (2015) CD40-TNF activation in mice induces extended sickness behavior syndrome co-incident with but not dependent on activation of the kynurenine pathway. *Brain, behavior, and immunity* 50:125–140. doi:10.1016/j.bbi.2015.06.184
- Cella M, Colonna M (2015) Aryl hydrocarbon receptor: Linking environment to immunity. *Seminars in immunology*. doi:10.1016/j.smim.2015.10.002
- Curzon G (1969) Tryptophan pyrrolase--a biochemical factor in depressive illness? *The British journal of psychiatry : the journal of mental science* 115 (529):1367–1374 [PubMed: 4902183]
- Curzon G, Bridges PK (1970) Tryptophan metabolism in depression. *Journal of neurology, neurosurgery, and psychiatry* 33 (5):698–704
- Dantzer R (2001) Cytokine-induced sickness behavior: where do we stand? *Brain, behavior, and immunity* 15 (1):7–24. doi:10.1006/brbi.2000.0613
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience* 9 (1):46–56. doi:10.1038/nrn2297 [PubMed: 18073775]
- Dantzer R, Walker AK (2014) Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? *J Neural Transm (Vienna)* 121 (8):925–932. doi:10.1007/s00702-014-1187-1 [PubMed: 24633997]
- De Bandt JP, Cynober L (2006) Therapeutic use of branched-chain amino acids in burn, trauma, and sepsis. *The Journal of nutrition* 136 (1 Suppl):308S–313S [PubMed: 16365104]
- Fatokun AA, Hunt NH, Ball HJ (2013) Indoleamine 2,3-dioxygenase 2 (IDO2) and the kynurenine pathway: characteristics and potential roles in health and disease. *Amino acids* 45 (6):1319–1329. doi:10.1007/s00726-013-1602-1 [PubMed: 24105077]
- Fernstrom JD (1981) Dietary precursors and brain neurotransmitter formation. *Annual review of medicine* 32:413–425. doi:10.1146/annurev.me.32.020181.002213
- Fernstrom JD, Wurtman RJ (1971) Brain serotonin content: physiological dependence on plasma tryptophan levels. *Science* 173 (3992):149–152 [PubMed: 5581909]
- Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences* 908:244–254 [PubMed: 10911963]
- Frenois F, Moreau M, O'Connor J, Lawson M, Micon C, Lestage J, Kelley KW, Dantzer R, Castanon N (2007) Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. *Psychoneuroendocrinology* 32 (5):516–531. doi:10.1016/j.psyneuen.2007.03.005 [PubMed: 17482371]
- Fromentin G, Darcel N, Chaumontet C, Marsset-Baglieri A, Nadkarni N, Tome D (2012) Peripheral and central mechanisms involved in the control of food intake by dietary amino acids and proteins. *Nutrition research reviews* 25 (1):29–39. doi:10.1017/S0954422411000175 [PubMed: 22643031]

- Fu X, Lawson MA, Kelley KW, Dantzer R (2011) HIV-1 Tat activates indoleamine 2,3 dioxygenase in murine organotypic hippocampal slice cultures in a p38 mitogen-activated protein kinase-dependent manner. *Journal of neuroinflammation* 8:88. doi:10.1186/1742-2094-8-88 [PubMed: 21810259]
- Fukui S, Schwarcz R, Rapoport SI, Takada Y, Smith QR (1991) Blood-brain barrier transport of kynurenines: implications for brain synthesis and metabolism. *Journal of neurochemistry* 56 (6): 2007–2017 [PubMed: 1827495]
- Gibney SM, Fagan EM, Waldron AM, O'Byrne J, Connor TJ, Harkin A (2014) Inhibition of stress-induced hepatic tryptophan 2,3-dioxygenase exhibits antidepressant activity in an animal model of depressive behaviour. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum* 17 (6):917–928. doi: 10.1017/S1461145713001673
- Gibney SM, McGuinness B, Prendergast C, Harkin A, Connor TJ (2013) Poly I:C-induced activation of the immune response is accompanied by depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. *Brain, behavior, and immunity* 28:170–181. doi:10.1016/j.bbi.2012.11.010
- Godbout JP, Moreau M, Lestage J, Chen J, Sparkman NL, O'Connor J, Castanon N, Kelley KW, Dantzer R, Johnson RW (2008) Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 33 (10):2341–2351. doi: 10.1038/sj.npp.1301649 [PubMed: 18075491]
- Gracia-Rubio I, Moscoso-Castro M, Pozo OJ, Marcos J, Nadal R, Valverde O (2016) Maternal separation induces neuroinflammation and long-lasting emotional alterations in mice. *Progress in neuro-psychopharmacology & biological psychiatry* 65:104–117. doi:10.1016/j.pnpbp.2015.09.003 [PubMed: 26382758]
- Greenwood MH, Lader MH, Kantameneni BD, Curzon G (1975) The acute effects of oral (–)-tryptophan in human subjects. *British journal of clinical pharmacology* 2 (2):165–172 [PubMed: 1234498]
- Guillemin GJ, Smythe G, Takikawa O, Brew BJ (2005) Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia* 49 (1):15–23. doi:10.1002/glia.20090 [PubMed: 15390107]
- Heisler JM, O'Connor JC (2015) Indoleamine 2,3-dioxygenase-dependent neurotoxic kynurenine metabolism mediates inflammation-induced deficit in recognition memory. *Brain, behavior, and immunity* 50:115–124. doi:10.1016/j.bbi.2015.06.022
- Henry CJ, Huang Y, Wynne AM, Godbout JP (2009) Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1 β and anti-inflammatory IL-10 cytokines. *Brain, behavior, and immunity* 23 (3):309–317. doi:10.1016/j.bbi.2008.09.002
- Heyes MP, Saito K, Chen CY, Proescholdt MG, Nowak TS Jr., Li J, Beagles KE, Proescholdt MA, Zito MA, Kawai K, Markey SP (1997) Species heterogeneity between gerbils and rats: quinolinate production by microglia and astrocytes and accumulations in response to ischemic brain injury and systemic immune activation. *Journal of neurochemistry* 69 (4):1519–1529 [PubMed: 9326281]
- Jackman KA, Brait VH, Wang Y, Maghazal GJ, Ball HJ, McKenzie G, De Silva TM, Stocker R, Sobey CG (2011) Vascular expression, activity and function of indoleamine 2,3-dioxygenase-1 following cerebral ischaemia-reperfusion in mice. *Naunyn-Schmiedeberg's archives of pharmacology* 383 (5):471–481. doi:10.1007/s00210-011-0611-4
- Ji WW, Wang SY, Ma ZQ, Li RP, Li SS, Xue JS, Li W, Niu XX, Yan L, Zhang X, Fu Q, Qu R, Ma SP (2014) Effects of perillaldehyde on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. *Pharmacology, biochemistry, and behavior* 116:1–8. doi:10.1016/j.pbb.2013.10.026
- Kang A, Hao H, Zheng X, Liang Y, Xie Y, Xie T, Dai C, Zhao Q, Wu X, Xie L, Wang G (2011) Peripheral anti-inflammatory effects explain the ginsenosides paradox between poor brain distribution and anti-depression efficacy. *Journal of neuroinflammation* 8:100. doi: 10.1186/1742-2094-8-100 [PubMed: 21843370]

- Kaster MP, Gadotti VM, Calixto JB, Santos AR, Rodrigues AL (2012) Depressive-like behavior induced by tumor necrosis factor- α in mice. *Neuropharmacology* 62 (1):419–426. doi:10.1016/j.neuropharm.2011.08.018 [PubMed: 21867719]
- Kelley KW, O'Connor JC, Lawson MA, Dantzer R, Rodriguez-Zas SL, McCusker RH (2013) Aging leads to prolonged duration of inflammation-induced depression-like behavior caused by *Bacillus Calmette-Guerin*. *Brain, behavior, and immunity* 32:63–69. doi:10.1016/j.bbi.2013.02.003
- Kigerl KA, Ankeny DP, Garg SK, Wei P, Guan Z, Lai W, McTigue DM, Banerjee R, Popovich PG (2012) System x(c)[−] regulates microglia and macrophage glutamate excitotoxicity in vivo. *Experimental neurology* 233 (1):333–341. doi:10.1016/j.expneurol.2011.10.025 [PubMed: 22079587]
- Kim H, Chen L, Lim G, Sung B, Wang S, McCabe MF, Rusanescu G, Yang L, Tian Y, Mao J (2012) Brain indoleamine 2,3-dioxygenase contributes to the comorbidity of pain and depression. *The Journal of clinical investigation* 122 (8):2940–2954. doi:10.1172/JCI61884 [PubMed: 22751107]
- Kimura A, Naka T, Nakahama T, Chinen I, Masuda K, Nohara K, Fujii-Kuriyama Y, Kishimoto T (2009) Aryl hydrocarbon receptor in combination with Stat1 regulates LPS-induced inflammatory responses. *The Journal of experimental medicine* 206 (9):2027–2035. doi:10.1084/jem.20090560 [PubMed: 19703987]
- Kita T, Morrison PF, Heyes MP, Markey SP (2002) Effects of systemic and central nervous system localized inflammation on the contributions of metabolic precursors to the L-kynurenine and quinolinic acid pools in brain. *Journal of neurochemistry* 82 (2):258–268 [PubMed: 12124427]
- Lapin IP (1972) Interaction of kynurenine and its metabolites with tryptamine, serotonin and its precursors and oxotremorine. *Psychopharmacologia* 26 (3):237–247 [PubMed: 4672450]
- Lapin IP (1978) Stimulant and convulsive effects of kynurenines injected into brain ventricles in mice. *Journal of neural transmission* 42 (1):37–43 [PubMed: 641543]
- Lapin IP (1983) Antagonism of kynurenine-induced seizures by picolinic, kynurenic and xanthurenic acids. *Journal of neural transmission* 56 (2–3):177–185 [PubMed: 6864208]
- Laugeray A, Launay JM, Callebert J, Surget A, Belzung C, Barone PR (2010) Peripheral and cerebral metabolic abnormalities of the tryptophan-kynurenine pathway in a murine model of major depression. *Behavioural brain research* 210 (1):84–91. doi:10.1016/j.bbr.2010.02.014 [PubMed: 20153778]
- Lawson MA, Kelley KW, Dantzer R (2011) Intracerebroventricular administration of HIV-1 Tat induces brain cytokine and indoleamine 2,3-dioxygenase expression: a possible mechanism for AIDS comorbid depression. *Brain, behavior, and immunity* 25 (8):1569–1575. doi:10.1016/j.bbi.2011.05.006
- Lehnert H, Wurtman RJ (1993) Amino acid control of neurotransmitter synthesis and release: physiological and clinical implications. *Psychotherapy and psychosomatics* 60 (1):18–32 [PubMed: 7901866]
- Lestage J, Verrier D, Palin K, Dantzer R (2002) The enzyme indoleamine 2,3-dioxygenase is induced in the mouse brain in response to peripheral administration of lipopolysaccharide and superantigen. *Brain, behavior, and immunity* 16 (5):596–601
- Li R, Zhao D, Qu R, Fu Q, Ma S (2015a) The effects of apigenin on lipopolysaccharide-induced depressive-like behavior in mice. *Neuroscience letters* 594:17–22. doi:10.1016/j.neulet.2015.03.040 [PubMed: 25800110]
- Li Y, Eskelund AR, Zhou H, Budac DP, Sanchez C, Gulinello M (2015b) Behavioral Deficits Are Accompanied by Immunological and Neurochemical Changes in a Mouse Model for Neuropsychiatric Lupus (NP-SLE). *International journal of molecular sciences* 16 (7):15150–15171. doi:10.3390/ijms160715150 [PubMed: 26151848]
- Manosso LM, Neis VB, Moretti M, Daufenbach JF, Freitas AE, Colla AR, Rodrigues AL (2013) Antidepressant-like effect of alpha-tocopherol in a mouse model of depressive-like behavior induced by TNF- α . *Progress in neuro-psychopharmacology & biological psychiatry* 46:48–57. doi:10.1016/j.pnpbp.2013.06.012 [PubMed: 23816813]
- Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA (2010) An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *Journal of immunology* 185 (6):3190–3198. doi:10.4049/jimmunol.0903670

- Miura H, Ando Y, Noda Y, Isobe K, Ozaki N (2011) Long-lasting effects of inescapable-predator stress on brain tryptophan metabolism and the behavior of juvenile mice. *Stress* 14 (3):262–272. doi: 10.3109/10253890.2010.541539 [PubMed: 21294659]
- Moreau M, Andre C, O'Connor JC, Dumich SA, Woods JA, Kelley KW, Dantzer R, Lestage J, Castanon N (2008) Inoculation of *Bacillus Calmette-Guerin* to mice induces an acute episode of sickness behavior followed by chronic depressive-like behavior. *Brain, behavior, and immunity* 22 (7):1087–1095. doi:10.1016/j.bbi.2008.04.001
- Moreau M, Lestage J, Verrier D, Mormede C, Kelley KW, Dantzer R, Castanon N (2005) Bacille Calmette-Guerin inoculation induces chronic activation of peripheral and brain indoleamine 2,3-dioxygenase in mice. *The Journal of infectious diseases* 192 (3):537–544. doi:10.1086/431603 [PubMed: 15995970]
- Muller N, Myint AM, Schwarz MJ (2009) The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders--relation to drug treatment. *Dialogues in clinical neuroscience* 11 (3):319–332 [PubMed: 19877499]
- Munn DH, Mellor AL (2013) Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends in immunology* 34 (3):137–143. doi:10.1016/j.it.2012.10.001 [PubMed: 23103127]
- Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, Brown C, Mellor AL (1998) Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science* 281 (5380):1191–1193 [PubMed: 9712583]
- Norden DM, Devine R, Bicer S, Jing R, Reiser PJ, Wold LE, Godbout JP, McCarthy DO (2015a) Fluoxetine prevents the development of depressive-like behavior in a mouse model of cancer related fatigue. *Physiology & behavior* 140:230–235. doi:10.1016/j.physbeh.2014.12.045 [PubMed: 25554480]
- Norden DM, McCarthy DO, Bicer S, Devine RD, Reiser PJ, Godbout JP, Wold LE (2015b) Ibuprofen ameliorates fatigue- and depressive-like behavior in tumor-bearing mice. *Life sciences* 143:65–70. doi:10.1016/j.lfs.2015.10.020 [PubMed: 26498217]
- O'Connor JC, Andre C, Wang Y, Lawson MA, Szegedi SS, Lestage J, Castanon N, Kelley KW, Dantzer R (2009a) Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 29 (13):4200–4209. doi:10.1523/JNEUROSCI.5032-08.2009
- O'Connor JC, Lawson MA, Andre C, Briley EM, Szegedi SS, Lestage J, Castanon N, Herkenham M, Dantzer R, Kelley KW (2009b) Induction of IDO by bacille Calmette-Guerin is responsible for development of murine depressive-like behavior. *Journal of immunology* 182 (5):3202–3212. doi: 10.4049/jimmunol.0802722
- O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R (2009c) Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Molecular psychiatry* 14 (5):511–522. doi:10.1038/sj.mp.4002148 [PubMed: 18195714]
- Robinson CM, Hale PT, Carlin JM (2006) NF-kappa B activation contributes to indoleamine dioxygenase transcriptional synergy induced by IFN-gamma and tumor necrosis factor-alpha. *Cytokine* 35 (1–2):53–61. doi:10.1016/j.cyto.2006.07.007 [PubMed: 16931033]
- Rosario FJ, Kanai Y, Powell TL, Jansson T (2013) Mammalian target of rapamycin signalling modulates amino acid uptake by regulating transporter cell surface abundance in primary human trophoblast cells. *The Journal of physiology* 591 (Pt 3):609–625. doi:10.1113/jphysiol.2012.238014 [PubMed: 23165769]
- Ruhe HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular psychiatry* 12 (4):331–359. doi:10.1038/sj.mp.4001949 [PubMed: 17389902]
- Schwarz R, Bruno JP, Muchowski PJ, Wu HQ (2012) Kynurenines in the mammalian brain: when physiology meets pathology. *Nature reviews Neuroscience* 13 (7):465–477. doi:10.1038/nrn3257 [PubMed: 22678511]

- Sekine A, Okamoto M, Kanatani Y, Sano M, Shibata K, Fukuwatari T (2015) Amino acids inhibit kynurenic acid formation via suppression of kynurenine uptake or kynurenic acid synthesis in rat brain in vitro. *SpringerPlus* 4:48. doi:10.1186/s40064-015-0826-9 [PubMed: 25674503]
- Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG (2006) The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. *Molecular psychiatry* 11 (11):984–991. doi:10.1038/sj.mp.4001879 [PubMed: 16894392]
- Speciale C, Hares K, Schwarcz R, Brookes N (1989) High-affinity uptake of L-kynurenine by a Na⁺-independent transporter of neutral amino acids in astrocytes. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 9 (6):2066–2072
- Sulakhiya K, Kumar P, Jangra A, Dwivedi S, Hazarika NK, Baruah CC, Lahkar M (2014) Honokiol abrogates lipopolysaccharide-induced depressive like behavior by impeding neuroinflammation and oxido-nitrosative stress in mice. *European journal of pharmacology* 744:124–131. doi:10.1016/j.ejphar.2014.09.049 [PubMed: 25446914]
- Takikawa O (2005) Biochemical and medical aspects of the indoleamine 2,3-dioxygenase-initiated L-tryptophan metabolism. *Biochemical and biophysical research communications* 338 (1):12–19. doi:10.1016/j.bbrc.2005.09.032 [PubMed: 16176799]
- Taylor MW, Feng GS (1991) Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 5 (11):2516–2522 [PubMed: 1907934]
- Terness P, Bauer TM, Rose L, Dufter C, Watzlik A, Simon H, Opelz G (2002) Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. *The Journal of experimental medicine* 196 (4):447–457 [PubMed: 12186837]
- Thomas SR, Mohr D, Stocker R (1994) Nitric oxide inhibits indoleamine 2,3-dioxygenase activity in interferon-gamma primed mononuclear phagocytes. *The Journal of biological chemistry* 269 (20):14457–14464 [PubMed: 7514170]
- Tilleux S, Hermans E (2007) Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. *Journal of neuroscience research* 85 (10):2059–2070. doi:10.1002/jnr.21325 [PubMed: 17497670]
- Too LK, McQuillan JA, Ball HJ, Kanai M, Nakamura T, Funakoshi H, McGregor IS, Hunt NH (2014) The kynurenine pathway contributes to long-term neuropsychological changes in experimental pneumococcal meningitis. *Behavioural brain research* 270:179–195. doi:10.1016/j.bbr.2014.05.018 [PubMed: 24844751]
- Kumar Vijaya K, Rudra A, Sreedhara MV, Subramani Siva T, Prasad DS, Das ML, Murugesan S, Yadav R, Trivedi RK, Louis JV, Li YW, Bristow LJ, Naidu PS, Vikramadithyan RK (2014) Bacillus Calmette-Guerin vaccine induces a selective serotonin reuptake inhibitor (SSRI)-resistant depression like phenotype in mice. *Brain, behavior, and immunity* 42:204–211. doi:10.1016/j.bbi.2014.06.205
- Vilar-Pereira G, Silva AA, Pereira IR, Silva RR, Moreira OC, de Almeida LR, de Souza AS, Rocha MS, Lannes-Vieira J (2012) Trypanosoma cruzi-induced depressive-like behavior is independent of meningoencephalitis but responsive to parasiticide and TNF-targeted therapeutic interventions. *Brain, behavior, and immunity* 26 (7):1136–1149. doi:10.1016/j.bbi.2012.07.009
- Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, Dantzer R (2013) NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 38 (9):1609–1616. doi:10.1038/npp.2013.71 [PubMed: 23511700]
- Walker AK, Vichaya E, Wing E, Banks W, Dantzer R (2015) Leucine blocks lipopolysaccharide-induced depression like behavior by interfering with kynurenine influx into the brain. *Brain, behavior, and immunity* 49:e36
- Walker FR (2013) A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology* 67:304–317. doi:10.1016/j.neuropharm.2012.10.002 [PubMed: 23085335]

- Wang Z, Zhang Q, Yuan L, Wang S, Liu L, Yang X, Li G, Liu D (2014) The effects of curcumin on depressive-like behavior in mice after lipopolysaccharide administration. *Behavioural brain research* 274:282–290. doi:10.1016/j.bbr.2014.08.018 [PubMed: 25131506]
- Ward JL, Harting MT, Cox CS Jr., Mercer DW (2011) Effects of ketamine on endotoxin and traumatic brain injury induced cytokine production in the rat. *The Journal of trauma* 70 (6):1471–1479. doi: 10.1097/TA.0b013e31821c38bd [PubMed: 21817985]
- Xie W, Cai L, Yu Y, Gao L, Xiao L, He Q, Ren Z, Liu Y (2014) Activation of brain indoleamine 2,3-dioxygenase contributes to epilepsy-associated depressive-like behavior in rats with chronic temporal lobe epilepsy. *Journal of neuroinflammation* 11:41. doi:10.1186/1742-2094-11-41 [PubMed: 24594021]
- Yoshida R, Hayaishi O (1978) Induction of pulmonary indoleamine 2,3-dioxygenase by intraperitoneal injection of bacterial lipopolysaccharide. *Proceedings of the National Academy of Sciences of the United States of America* 75 (8):3998–4000 [PubMed: 279015]
- Yoshida R, Urade Y, Tokuda M, Hayaishi O (1979) Induction of indoleamine 2,3-dioxygenase in mouse lung during virus infection. *Proceedings of the National Academy of Sciences of the United States of America* 76 (8):4084–4086 [PubMed: 291064]
- Young SN (2013) The effect of raising and lowering tryptophan levels on human mood and social behaviour. *Philosophical transactions of the Royal Society of London Series B, Biological sciences* 368 (1615):20110375. doi:10.1098/rstb.2011.0375 [PubMed: 23440461]
- Zhou W, Dantzer R, Budac DP, Walker AK, Mao-Ying QL, Lee AW, Heijnen CJ, Kavelaars A (2015) Peripheral indoleamine 2,3-dioxygenase 1 is required for comorbid depression-like behavior but does not contribute to neuropathic pain in mice. *Brain, behavior, and immunity* 46:147–153. doi: 10.1016/j.bbi.2015.01.013
- Zhu X, Li P, Hao X, Wei K, Min S, Luo J, Xie F, Jin J (2015) Ketamine-mediated alleviation of electroconvulsive shock-induced memory impairment is associated with the regulation of neuroinflammation and soluble amyloid-beta peptide in depressive-like rats. *Neuroscience letters* 599:32–37. doi:10.1016/j.neulet.2015.05.022 [PubMed: 25980993]
- Zwilling D, Huang SY, Sathyaikumar KV, Notarangelo FM, Guidetti P, Wu HQ, Lee J, Truong J, Andrews-Zwilling Y, Hsieh EW, Louie JY, Wu T, Searce-Levie K, Patrick C, Adame A, Giorgini F, Moussaoui S, Laue G, Rassoulpour A, Flik G, Huang Y, Muchowski JM, Masliah E, Schwarcz R, Muchowski PJ (2011) Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* 145 (6):863–874. doi:10.1016/j.cell.2011.05.020 [PubMed: 21640374]

Fig. 1 –.

Experimental design for studying inflammation-induced depression in mice. Mice are injected with a sub-septic dose of lipopolysaccharide (LPS) at time 0, preceded or not by the treatment of interest (e.g., an anti-inflammatory compound). Their sickness behavior develops within a few hours and wanes off by 12–16 h post-LPS. Behavioral tests of depression are carried out 24 h after LPS administration, and tissues are collected immediately afterward to measure biomarkers of inflammation and kynurenine metabolism.

**What have we learned from the study of inflammation-induced depression?
(1) Symptoms of depression emerge on a background of sickness**

(Capuron L, Miller AH, Pharmacol Therap, 2011)

Fig. 2 -

Time course of the development of symptoms of depression in response to interferon (IFN)- α in patients with cancer. Time is represented in weeks (W). Note that neurovegetative symptoms (including reduced appetite, sleep disorders, and fatigue) emerge first in response to repeated injections of IFN- α , whereas mood and cognitive symptoms emerge later. IFN- α -induced symptoms of depression differ in their response to antidepressant treatment. Neurovegetative symptoms appear in all patients, whereas mood and cognitive symptoms appear only in one third to one half of patients who have vulnerability factors, represented, for instance, by single nucleotide polymorphisms of proinflammatory and anti-inflammatory genes (adapted from (Capuron and Miller 2011)).

Fig. 3 -
Schematic representation of the tryptophan, kynurenine, and serotonin metabolism pathways. The enzymes for which the activity is modulated by inflammation are labeled in red. Pathways represented by two arrows involve several metabolites and enzymatic reactions.

I. Tryptophan starvation hypothesis

- Decreased bioavailability of tryptophan as a consequence of the increased metabolism of tryptophan into kynurenine

I. Kynurenine metabolism pathway

- Increased intracellular transport of tryptophan compensating for decreased extracellular tryptophan
- Interaction of kynurenine with ARH
- Formation of cytotoxic kynurenine metabolites (3-hydroxy kynurenine, quinolinic acid)

Fig. 4 –.

The various hypotheses proposed to account for the effect of activation of indoleamine 2,3 dioxygenase and the kynurenine pathway on immune functions.

Fig. 5 –.

Pathophysiology of inflammation-induced depression. Activation of innate immunity by binding of pathogen-associated molecular patterns (e.g., lipopolysaccharide) to Toll-like receptors and inflammasome elements induce the production and release of proinflammatory cytokines at the periphery, which in turn recruit immune-to-brain communication pathways and activate microglia. Activated microglia produce and release proinflammatory cytokines that organize the sickness response to pathogen-associated molecular patterns (not represented in the figure). Activation of indoleamine 2,3 dioxygenase at the periphery increases kynurenine that is transported into the brain by LAT1 and metabolized into neurotoxic kynurenine metabolites (e.g., quinolinic acid) at the level of activated microglia via a series of enzymatic reactions initiated by mitochondrial kynurenine monooxygenase. Quinolinic acid alone or in combination with extracellular glutamate released by activated microglia activates N-methyl-D-aspartate receptors.