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Inflammation-induced depression: Its pathophysiology and therapeutic implications

Sang Won Jeon[1], Yong-Ku Kim[2*]

[1]Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[2]Department of Psychiatry, College of Medicine, Korea University, Ansan Hospital, Ansan, Republic of Korea

[Running head: inflammation-induced depression]

[*]Address for correspondence:

Yong-Ku Kim, MD, PhD, Professor, Department of Psychiatry, College of Medicine, Korea University, Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, 15355, Republic of Korea

Tel.: +82-31-412-5140, Fax: +82-31-412-4930, E-mail: yongku@korea.edu

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Abstract

Inflammation is not the only cause of depression and cannot explain its entire pathophysiology, but it is an important pathogenic factor that explains one possible mechanism of depression, with the kynurenine (KYN) pathway of tryptophan at its center. In particular, greater impairment seems to exist in the KYN pathway in inflammation-induced depression related to immunotherapy, autoimmune disease, and infection. In patients with these conditions, immunopharmacology is likely to be an important therapy. To develop this therapy, clear evidence of the immune-KYN pathway must be established via multiple types of experiments. This paper reviews the body of evidence, not only for the action of tryptophan (TRY) and consequent serotonin depletion, but also for the detrimental effects of TRY catabolites and the key enzymes in the KYN pathway that play important roles in the pathophysiology of inflammation-induced depression. In addition, this paper explores a potential treatment strategy for inflammation-induced depression using KYN metabolism.

Keywords: depression, inflammation, tryptophan, kynurenine pathway, immunopharmacology

1. Introduction

Depression is a brain disorder expressed by the interactions of various heterogeneous pathogenic mechanisms, and it has been argued that inflammation can cause depression. This perspective is based on studies showing that patients with infectious or autoimmune diseases that were undergoing cytokine therapy had a relatively high incidence of depression, and that inflammatory markers were elevated in patients with depression who were without any physical disease (Zunszain et al., 2013). The fatigue and depressive symptoms that occur in nearly 90% of patients receiving interferon (IFN) treatment for hepatitis C or cancer are further strong evidence of this relationship between inflammation and depression. More than 50% of patients treated with high-dose IFN-α met the diagnostic criteria for major depressive disorder (MDD) within 3 months of starting treatment (Musselman et al., 2001), and interleukin (IL)-6 and tumor necrosis factor (TNF)-α were both elevated after the administration of IFN-α, showing a clear association with severity of depression symptoms (Capuron et al., 2002). It was reported that the depressive symptoms caused by IFN-α administration depend on the polymorphism of the serotonin transporter (5-HTT) and IL-6 genes (Bull et al., 2009) and that depression symptoms occur because IFN-α lowers the serotonin utilization rate by increasing the activation of indoleamine 2,3-dioxygenase (IDO), which is a pro-inflammatory cytokine (Raison et al., 2009).

Depression, however, has many more multifactorial characteristics than a primary inflammatory disease, and hyperactivity of the inflammatory response is not specific to depression (Myint and Kim, 2014). Stress obviously increases pro-inflammatory cytokines, but it is difficult to say that the inflammatory markers extracted from plasma represent the state of the entire central nervous system. It is also uncertain whether increased inflammation

causes depression or is a result of it. This uncertainty arises partly because depression is currently diagnosed only through interviews regarding a subject's phenomenological symptoms, which precludes control of subjects' intrinsic heterogeneity for measurement purposes, as well as control of the various environmental factors involved.

Although inflammation is not a specific finding for depression, it accounts for a large part of the pathophysiology of depression, especially in inflammation-induced depression. Immune-modulating medication is a very effective treatment for this type of depression (Loftis et al., 2010). In this paper, we examine the kynurenine (KYN) pathway of tryptophan (TRY), which is central to inflammation-induced depression. We investigate the roles of the enzymes and metabolites in and around the KYN pathway and how they affect depression, and we explore possible therapies for related depression.

2. Methods

The source of the literature we reviewed was the electronic database MEDLINE (1950–2017). The initial search was for combinations of the following thesaurus terms: [depression/ major depressive disorder] AND [kynurenine/ kynurenine pathway/ inflammatory state/ tryptophan metabolite (catabolite)]. The inclusion criteria were (i) studies examining immune-kynurenine mechanisms underlying depression in human subjects, (ii) studies examining immune-kynurenine mechanisms underlying depression in patients with inflammatory conditions, (iii) review articles on neuroinflammation and depression, and (iv) articles written in English. The exclusion criteria were (i) letters to editors and editorials without data and (ii) studies outside the time window (1950–2017), because these were not available electronically. We reviewed the titles of all citations meeting these criteria, and we

retrieved relevant abstracts for more detailed evaluation. When there was uncertainty, we studied the full paper. We also hand searched the references listed in relevant studies and reviews to identify additional studies to consider for inclusion. We identified 675 references, and we included 83 of them in this review.

3. TRY Metabolism

TRY is obtained from dietary sources and is an essential amino acid with an indole ring structure (Eynard et al., 1993). About 50–85% of plasma TRY is bound to albumin, and this bond is easily broken because it is unstable (Yuwiler et al., 1977). TRY competes with large amino acids (LAAs) to pass the blood brain barrier (BBB), and the degree of TRY's competition with LAAs mainly determines its central availability in the brain. Meanwhile, it is also determined in part by cerebral demand (Fernstrom, 1977).

The metabolism of TRY has two major pathways: the methoxyindole and KYN pathways. These two pathways compete for KYN as their initial substrate. Approximately 1–5% of the available TRY in the body is synthesized as serotonin (5-HT) via the methoxyindole pathway. This serotonin synthesis occurs mainly in the gut enterochromaffin cells, and 10–20% of the TRY passes through the BBB, with serotonin synthesis occurring in the brain (Gal and Sherman, 1980). Additionally, about 95–99% of the TRY is metabolized to the KYN pathway, which forms important metabolites that explain various pathophysiologies of depression while forming many metabolites. Much of the flow into the KYN pathway occurs when TRY is metabolized by tryptophan 2,3-dioxygenase (TDO) in the liver. In normal physiologic conditions, because the activity of TDO is controlled mainly by the tryptophan level itself, the activity of TDO is generally stabilized, and the KYN pathway

is also well stabilized (Watanabe et al., 1980).

4. The Methoxyindole Pathway

Because less than 5% of TRY is metabolized to the methoxyindole pathway, the availability of TRY, the substrate of serotonin, is an important rate-limiting factor for serotonin synthesis (Gal and Sherman, 1980). Another rate-limiting step is the catabolization of TRY to 5-hydroxytryptophan (5-HTP) by TRY-hydroxylase. If subsequent decarboxylation occurs, 5-HT is produced and becomes the substrate of melatonin. The rate-limiting step of melatonin synthesis is the formation of N-acetyl-serotonin (NAS) by 5-HT-N-acetylation (Kopin et al., 1961). NAS was seen in the past as an intermediate product in the process of synthesis from serotonin to melatonin, but at present, it is seen as having a distinct role in the central nervous system (Brown et al., 1984). NAS is changed into 5-methoxy-nacetyltryptamine (melatonin) via subsequent O-methylation. Thus, serotonin depletion affects the reduction of NAS and melatonin production, in addition to affecting the serotonin receptor function. A lack of 5-HT, and melatonin appears in MDD patients as symptoms of depressed mood (McIntyre et al., 1986; Coppen and Doogan, 1988), sleep disturbance (Brzezinski et al., 2005), and altered circadian rhythms (Oxenkrug and Requintina, 2003).

5. The KYN Pathway Without Immune Challenges

Figure 1 shows an overview of the tryptophan breakdown metabolic pathway under general physiologic conditions without activation of inflammation.

5.1 TRY conversion into KYN by TDO and IDO

Most TRY forms kynurenine (KYN) through the rate-limiting enzyme TDO in the liver, and IDO, another rate-limiting enzyme, also produces KYN (Maes et al., 2011). Both TDO and IDO commonly metabolize TRY into KYN, but they differ in their distributions in the body and have slightly different ways of activation. Although TDO is mainly distributed in the liver, IDO is mainly distributed in the extrahepatic tissues, including the brain. The astrocytes, microglia, microvascular endothelial cells, and macrophages are the places where IDO is mainly distributed (Gal and Sherman, 1980; Hayaishi, 1976). IDO is activated by pro-inflammatory cytokines (Carlin et al., 1987), and TDO can be activated by glucocorticoids (Salter and Pogson, 1985). Quantitatively, most TRY is metabolized by TDO in the liver, but because IDO is important in the brain, it is a key enzyme involved in inflammation-induced depression.

5.2 Post-KYN metabolism

KYN is metabolized into two distinct routes: the KYN-kynurenic acid (KYNA) pathway and the KYN-nicotinamide adenine dinucleotide (NAD) pathway. These two routes compete for the substrate KYN.

5.3 The KYN-NAD pathway

KYN is catabolized into 3-hydroxykynurenine (3OH-KIN) by the kynurenine-3-monooxygenase (KMO) enzyme, and 3OH-KIN is catabolized into 3-hydroxyanthranilic acid (HAA) by kynureninase. The subsequent catabolism proceeds along two routes: a pathway that proceeds as the complete oxidation pathway and produces adenosine triphosphate (ATP)

in the liver, and another pathway in which it is degraded into quinolinic acid (QUIN)-NAD-nicotinic acid, in that order. In the complete oxidation pathway producing ATP in the liver, a small amount of picolinic acid (PIC) is produced in addition to ATP. Under general conditions, the catabolism is carried out predominantly to form ATP, and the NAD formation is minor (Leklem, 1971). QUIN and picolinic acid are known to have anxiogenic effects because they affect the benzodiazepine receptor, as has been determined in experimental models (Lapin, 2003).

Because the formation of ATP in the cells is dependent on NAD, NAD is essential for cell maintenance. In the case of a depletion of NAD, the cells become vulnerable, which is fatal to the cells if they are stressed. Under physiologic conditions, to obtain this important NAD, QUIN as the substrate of NAD is only temporarily present in liver hepatocytes, and most of it is catabolized immediately to NAD, so there is little accumulation of QUIN in the liver (Bender, 1989). In summary, the KYN pathway is important for glycogen storage, which is done through the complete oxidation pathway in the brain and is important for supplying the small amount of NAD essential to the central nervous system (Leklem, 1971).

5.4 The KYN-KYNA pathway

The KYN-KYNA pathway is the process by which KYN is formed into KYNA by KYN-amino-transferases (KATs; Guidetti et al., 2007). The metabolism of this pathway in the liver is known to be greatly influenced by age and gender (Oxenkrug, 2010). Thus, depending on age and gender, the KYN-KYNA pathway becomes more stable or less stable and affects the competitive KYN-NAD pathway. KYNA contributes to the crosstalk of the KYN pathway and melatonin by inhibiting 5-HT-N-acetylation, a rate-limiting step for melatonin synthesis (Zawilska et al., 1997).

5.5 The KYN pathway in the brain

About 40% of the KYN used in the brain is KYN generated from TRY in the brain, and the remaining 60% is extra KYN that passed the BBB from the periphery (Gal and Sherman, 1980). In the brain, the catabolism of TRY and KYN occur mainly in the astrocytes and microglia (Grant et al., 2000). Although some brain neurons have IDO or TDO (Miller et al., 2004), the neurons are not the primary sites for the KYN pathway. Microglia and macrophages mainly produce QUIN. However, astrocytes lack KMO enzymes, and so the KYN-KYNA route is mainly activated, and KYNA is mainly produced (Guillemin et al., 2001; Guillemin et al., 2005). In addition, astrocytes metabolize the QUIN produced by the surrounding microglia (Guillemin et al., 2001).

6. The KYN Pathway in Immune Challenges

Figure 1 shows the tryptophan breakdown metabolic pathway under inflammatory conditions.

6.1 IDO activation by pro-inflammatory cytokines and TDO activation by glucocorticoid

Pro-inflammatory cytokines activate IDO enzymes, which are mainly distributed in extrahepatic tissues, including the blood, spleen, kidneys, lungs, and brain (Carlin et al., 1987). The pro-inflammatory cytokines that activate the IDO enzymes include IFN-γ, TNF-α, and IFN-α. IFN-γ is the strongest of these (Widner et al., 2000). Anti-inflammatory cytokines

inhibit IDO, such as IL-4 (Musso et al., 1994). Thus, in an inflammatory state or infectious condition, TRY metabolism shifts from the liver to the extrahepatic side due to IDO activation. In the inflammatory state, the KYN pathway is particularly active in the blood and lymphoid tissues, among the extrahepatic tissues (Moffett and Namboodiri, 2003).

The TDO enzyme is mainly activated by TRY, the substrate of TDO, but is also activated by cortisol (Salter and Pogson, 1985). During stress or inflammation, cortisol secretion is enhanced, TDO is activated, and KYN formation is increased. Because the liver cell uptake of KYN is not efficient for extrahepatic KYN, the further KYN pathway mainly occurs extrahepatically.

Finally, in a stress or inflammatory state, as pro-inflammatory cytokines and cortisol are increased and activate IDO and TDO, respectively, the formation of KYN is increased. Because KYN can pass through the BBB, the extra amount of peripheral KYN produced by the activation of IDO and TDO is supplied to the brain, which further activates KYN metabolism in the brain's astrocytes and microglia. As a result, the KYN pathway is highly activated in the brain.

6.2 TRY shunt toward the formation of KYN as a cause of serotonin deficiency

During stress or inflammation, the increased pro-inflammatory cytokines activate IDO, and the increased cortisol activates TDO. As a result, the production of KYN is increased, and the methoxyindole pathway is shifted toward the KYN pathway. In particular, TRY availability for serotonin synthesis in the brain becomes lower because the IDO that is predominantly distributed in the brain is activated (Myint and Kim, 2014). Moreover, the activated IDO accelerates the degradation of serotonin into formyl-5-hydroxykynuramine

(f5OHKYM), in addition to the degradation of the serotonin into 5-hydroxyindoleacetic acid (5HIAA) by monoamine oxidase (MAO; Pertz and Back, 1988). This further exacerbates serotonin deficiency, which affects the neurotransmission of norepinephrine, dopamine, and melatonin, and consequently causes depression because the catecholamines interact and are linked to one another (Schildkraut, 1995). IDO may also facilitate the degradation of melatonin into N-acetyl-N-formyl-5methoykynuramine (AFMK; de Almeida et al., 2003; Rozov et al., 2003). Therefore, in an inflammatory state, serotonin as the substrate of melatonin becomes insufficient, and melatonin production is also decreased. Additionally, melatonin degradation is accelerated by IDO, resulting in melatonin deficiency.

Meanwhile, 3OH-KIN is known to increase MAO activity (Van der Vliet and Bast, 1992). Therefore, if 3OH-KIN is increased due to a highly activated KYN pathway, it will promote the degradation of serotonin and catecholamines and will reduce their concentrations. Such serotonin depletion and changes in catecholamines are well known in the serotonin and monoamine hypothesis as causes of depression.

The process of serotonin synthesis deficiency according to a shift of the metabolism of TRY to the KYN pathway represents a vicious cycle. The production of cortisol by the adrenal glands is inhibited by 5-HT in the brain (“amygdaloid complex”; Lapin and Oxenkrug, 1969). As deficient 5-HT weakens inhibition of the brain–adrenal axis, the production of cortisol is increased. Increased cortisol super-induces TDO, and the activated TDO causes TRY to be metabolized more often into KYN. As a result, the availability of TRY for synthesizing 5-HT is significantly reduced. Consequently, this vicious cycle sustains the serotonin deficiency (Lapin and Oxenkrug, 1969).

5-HT (not competitively), NAS, and melatonin (competitively) inhibit liver TDO (Walsh and Daya, 1997). If 5-HT synthesis is lowered as the KYN pathway is activated, the

inhibition of TDO in the liver is weakened and TDO is further activated, leading to another vicious cycle in which the KYN pathway is again activated.

6.3 Imbalance between 3OH-KIN and KYNA

Pro-inflammatory cytokines enhance KMO activity in addition to IDO activity (Mellor and Munn, 1999). Therefore, in an inflammatory state, the production of 3OH-KIN becomes greater than that of KYNA, and the balance between 3OH-KIN and KYNA shifts from the KYNA side to the 3OH-KIN side. This imbalance is active in activated monocytes in the inflammatory state (Chiarugi et al., 2001). As a result, an increase in 3OH-KIN leads to an increase in the production of the next metabolite, QUIN. In other words, inflammation results in a state of imbalance between KINA with a neuroprotective effect, and 3OH-KIN and QUIN with neurodegenerative effects (Myint and Kim, 2014).

6.4 KIN metabolites (neurodegenerative vs. neuroprotective)

The N-methyl-D-aspartate (NMDA) agonists—QUIN and picolinic acid—are produced in the KYN-NAD pathway (Bender and McCreanor, 1985), and the free-radical generators—3-hydroxykynurenine (3OH-KIN) and 3-hyroxyanthranilic acid (HAA)—are generated (Okuda et al., 1998). Because picolinic acid is a metabolite that is produced in small amounts, QUIN is more important as an NMDA agonist than picolinic acid, and 3OH-KIN is more important as a free-radical generator than HAA because the substrate of HAA is 3OH-KIN.

KYNA is the only known endogenous antagonist to NMDA receptors (Perkins and Stone, 1982). Thus, KYNA, similarly to the exogenous NMDA antagonist, ketamine and MK-

801, might exert antidepressant (Zarate et al., 2005) and psychomimetic effects (Krystal et al., 1994). KINA also has a higher affinity and antagonistic effect on alpha-7-nicotine acetylcholine receptors (α7nAchR); Hilmas et al., 2001). Increase in KINA would induce antagonistic effect on α7nAchR that in turn would induce disturbance in cognitive functions or psychotic symptoms (Muller and Schwarz, 2008; Pocivavsek et al., 2011).

KYN metabolites contribute to the occurrence of direct neuroprotective–neurodegenerative changes in the brain by influencing several neurotransmissions. The accumulation of the NMDA agonist QUIN leads to excitotoxic neurodegenerative changes in the brain (Schwarcz et al., 1983). The increased formation of NMDA agonists induces a hyper glutamatergic status associated with depression (Muller and Schwarz, 2008). Hippocampal atrophy, which is frequently observed in depression, may be related to the activation of these QUINs (Wichers and Maes, 2004). KYNA, an NMDA antagonist, counteracts the excitotoxicity of QUIN to protect the hippocampus (Kim and Choi, 1987). The excitotoxicity of QUIN is also known to impair physiological negative-feedback regulation of the HPA axis because it results in the loss of corticosteroid receptors (Wichers and Maes, 2004). QUIN seems to partially contribute to the impairment of these negative HPA axis feedback circuits, which are frequently involved in depression.

3-hydroxykynurenine (3OH-KIN), a free-radical generator, highly produces reactive oxygen species (ROS) and causes neuronal apoptosis in the brain (Okuda et al., 1998). If ROS is produced in large amounts, it not only causes cell apoptosis but also changes cell membrane viscosity, resulting in a negative influence on the density of monoamine surface receptors, including the serotonin receptors (Van der Vliet and Bast, 1992).

In the inflammatory state, the balance between 3OH-KIN and KYNA shifts from the KYNA side to the 3OH-KIN side, but because of the general increase of KIN, KYNA also

increases more in the inflammatory state than in the normal state. This increased KYNA complements the negative effect of QUIN and maintains homeostasis of NMDA receptors. If the inflammatory state becomes chronic or intense, however, the balance of these KIN metabolites will collapse, leading to a disturbance of neurotransmission and to the neurodegenerative changes in the brain associated with depression (Myint and Kim, 2014). The imbalance of these neuroprotective and neurotoxic metabolites in MDD patients has been well-verified in human studies. The ratio between KYNA and KYN (KYNA/KYN) indicates how much KYN is degraded into KYNA, and this ratio was significantly lower in depression patients compared to a normal population (Myint et al., 2007). This pro-inflammatory cytokine-induced KYN imbalance is thought to partially contribute to the occurrence of neurodegenerative changes and to the loss of astrocytes, which are frequently reported in MDD patients (Myint et al., 2007).

If an imbalance in the KIN metabolites occurs as the inflammation becomes severe, the astrocyte–microglia–neuronal network, which has been protected by KYNA, becomes vulnerable to external environmental stimuli, such as stress. Neurotoxic metabolites, such as 3OH-KIN, cause multiple neuronal apoptosis events, including astrocytes and microglia, which makes the glial–neuronal network more vulnerable. This vulnerable glial–neuronal network further aggravates the neurodegenerative changes by reducing the synthesis of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF; Kim et al., 2016). The glial–neuronal network that becomes vulnerable through this mechanism seems to be a cause of recurrent and chronic MDD (Myint and Kim, 2003). Evidence for this is the fact that these metabolic imbalances are not corrected even after 6 weeks of selective serotonin reuptake inhibitor (SSRI) administration in depressed patients (Myint et al., 2007). Because exposure to long-term neurotoxic metabolites in the brain results in irreversible

neurodegenerative changes, which are not corrected by simple antidepressants, MDD is recurrent and becomes chronic. Therefore, manipulation related to the KYN pathway may be an important therapeutic approach to treat recurrent and chronic MDD patients.

7. IFN-α Treatment and Depression

IFN-α-therapy-induced depression in patients was associated with increased IL-6, decreased KYNA, and increased KYN/KYNA (Wichers et al., 2005). In another study, although the ratio of KYNA to QUIN was not specified, both KYNA and QUIN were reported to be increased in patients treated with IFN-α (Raison et al., 2010). In patients treated with IFN-α, cognitive disturbance was a common feature and may be a symptom caused by an enhanced antagonistic effect on α7nAchR due to increased KYNA (Pocivavsek et al., 2011). Several studies have shown slightly different results in patients treated with IFN-α therapy, such as increased or decreased KIN metabolites, but the common results are enhanced TRY degradation and changes in KYN metabolites after immune challenge with INF-α. It is common for these changes to be associated with depressive episodes.

IFN-γ is the most potent pro-inflammatory cytokine that activates IDO (Widner et al., 2000). Furthermore, because INF-γ is also known to stimulate 3-hydroxylase and kynureninase in the KYN-NAD pathway (Alberati-Giani et al., 1996), it activates the KYN pathway most prominently. Systemically administered INF-α passes through the BBB, and if it reaches an effective concentration, it acts on microglial cells or macrophage receptors (Sweeten et al., 2001). IFN-α, however, is much weaker than IFN-γ with respect to activating IDO, but because it has an effect of stimulating the production of other pro-inflammatory cytokines, such as IFN-γ and TNF-α, it ultimately has greater potency for activating IDO and

the KYN pathway (Robinson et al., 2005; Taylor and Grossberg, 1998). These mechanisms seem to be important for the development of inflammation-induced depression in patients undergoing INF-α therapy (Figure 2).

8. Kynurenine metabolites and suicidal behavior

There is accumulating evidence that the kynurenine pathway and TRY catabolites have been associated specifically with suicidal behavior. An increase in the levels of QUIN, the NMDA receptor agonist, and a decrease in neuroprotective tryptophan catabolites have been observed in suicidal patients (Bryleva et al., 2017). In the cerebrospinal fluid of patients with suicidal behavior, levels of QUIN and inflammatory cytokines were elevated compared to healthy controls (Erhardt et al., 2013; Bay-Richter et al., 2015). It is reported that QUIN staining was increased in postmortem brain sections in patients with severe depression who committed suicide (Steiner et al., 2011). The QUIN's agonistic effect on NMDA receptor could be a neurobiological mechanism underlying suicidal behavior (Bryleva et al., 2017). The rapid anti-suicidal effect of ketamine, an NMDA antagonist, could be due to its action on the similar biological mechanism. The mechanisms of tryptophan catabolites to cause suicidality have yet to be fully described, but is likely due to differential activity of the involved enzymes in patients. As knowledge in these areas is rapidly growing, targeting the tryptophan catabolites may provide attractive therapeutic approaches for managing suicidality.

9. The KYN Pathway as a Potential Strategy for the Treatment of Depression

The above results imply that immune activation, TRY metabolism, and the KYN pathway are important pathophysiologies in MDD patients. The manipulation of these

metabolic pathways will be a future treatment target for MDD and will be of much interest, especially for those patients with inflammation-induced MDD. To date, however, the data that have been gathered for the development of a new therapeutic strategy related to KYN metabolism are not sufficient. There are two broad categories of methods that can be applied to treatment: direct manipulation of the KYN metabolites and indirect manipulation of the pro-inflammatory cytokines or inflammation.

Several enzyme inhibitors associated with the KYN pathway may already be applicable to the treatment of MDD patients. However, if the metabolites are enhanced or blocked for reduction, their balance and interaction with other metabolites may be compromised. Therefore, clear evidence is needed regarding how the changes or ratios of metabolites are affected during such manipulations. Blocking the IDO or KMO enzymes may inhibit the formation of neurotoxic metabolites, such as 3OH-KIN or QUIN. However, these manipulations may cause hypofunction of NMDA receptors primarily, and may increase KYNA secondarily. Because KYNA is an NMDA antagonist, increased KYNA will further exacerbate NMDA receptor hypofunction. As a result, the cognitive functions may worsen or psychotic symptoms may be induced. Also, close monitoring of metabolites is required during manipulation. As discussed above, the KYN pathway has sensitive and complex crosstalk between the peripheral and central nervous systems. Therefore, both peripheral and direct biomarkers are required to precisely observe changes in the brain (the center). If these biomarkers are developed, they may be used, not only for therapeutic monitoring, but also for depression screening, antidepressant selection, and decision-making regarding treatment response.

To modulate the KYN pathway, anti-inflammatory cytokines or an anti-cytokine antibody such as TNF inhibitors may be applied as therapies. However, these manipulations

are not specific only to the KYN pathway, but also have systemic influences on both the peripheral and central nervous systems. Thus, it is still unknown whether this influence will be strong enough to treat depression.

The potential pharmacological interventions known to date in identified subjects are as follows. Given that fluoxetine, a SSRI, and bupropion, a dopamine enhancer, are known to inhibit pro-inflammatory cytokine production (Brustolim et al., 2006; Kenis and Maes, 2002), these universal antidepressant treatments may still be effective. Therapies that add a COX-2 inhibitor (celecoxib) to antidepressants have already been attempted, and the results have been reported (Muller et al., 2006).

It has recently become apparent that SSRIs have significant anti-inflammatory properties on microglia, the principal cells within the brain that respond to inflammatory factors (Tynan et al., 2012). The specific biological mechanisms of SSRI to modulate the microglial inflammatory response have yet to be fully described. Thus far a variety of possible mechanisms have been researched such as mediated effects via 5-HTT, cyclic adenosine monophosphate signaling, the transcription factor NF-κB, and the anti-inflammatory cytokine IL-10 (Walker, 2013). It has been also reported that serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine possess anti-inflammatory properties in mixed glial cultures (Bielecka et al., 2010). The evidence also exists supporting the notion that even some antipsychotics such as risperidone can exhibit significant anti-inflammatory effects (Kato et al., 2007). However, these medications including SSRI and SNRI have been optimized not for their anti-inflammatory capacity, but for their action on neurotransmitter system. The challenge now, is to increase the pharmacological evidence for the immunomodulatory properties of these medications.

The omega-3-fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic

acid (DHA), have both antidepressant and numerous anti-inflammatory properties by antagonizing membrane arachidonic acid formation, inhibiting COX-2 enzyme activity, and reducing prostaglandin E2 synthesis (Su, 2009), which down-regulate the IDO enzymes and its downstream metabolites (Cesario et al., 2011). EPA have been found to be effective in the prevention of IFN-induced depression (Su et al., 2014).

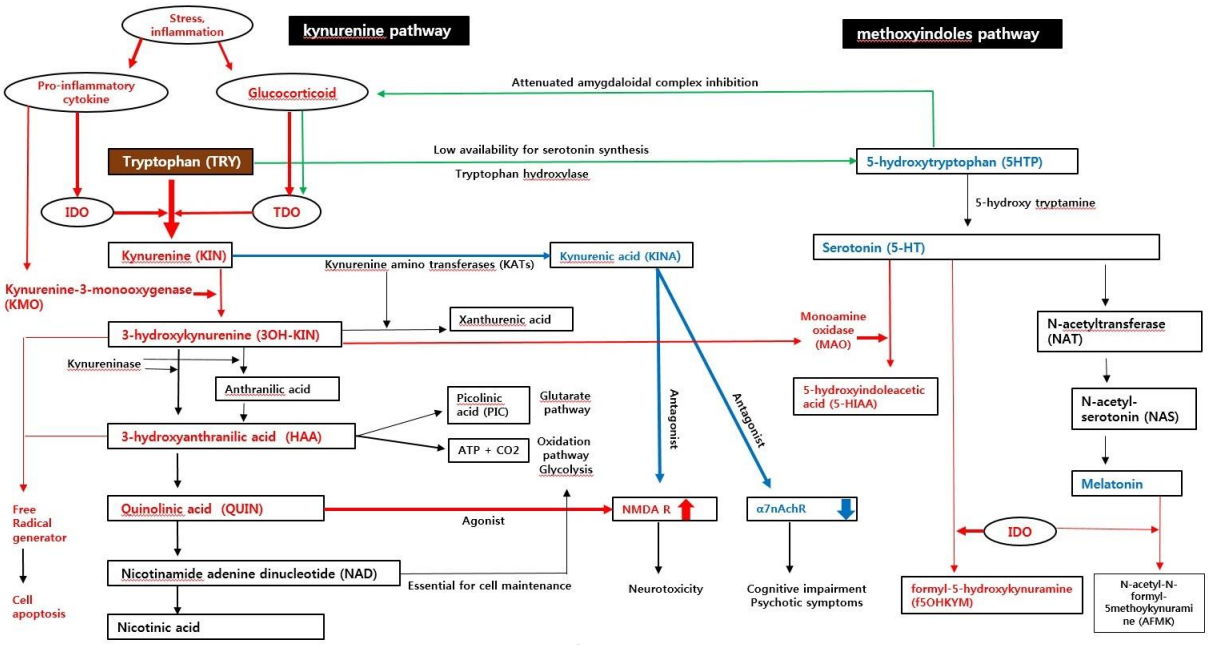
The effects on depression of antibodies to TNF-α (e.g., infiximab, etanercept) or antibodies to INF-γ, which inhibit cytokine production, have been reported (Skurkovich and Skurkovich, 2006). MAO inhibitors (Oxenkrug, 1991), minocycline (Ryu et al., 2006), and 1-methyl-L-TRY (Cady and Sono, 1991) are known to inhibit IDO activity. Finally, the administration of methoxyindoles (especially melatonin) has been reported to modulate the KYN pathway because they have the effect of inhibiting cortisol and the pro-inflammatory cytokines. Methoxyindoles have also been found to attenuate the excitatory and glutamate-mediated responses caused by the metabolites in the KIN pathway (Lapin et al., 1998; Prakhie and Oxenkrug, 1998).

10. Conclusions and Future Directions

Inflammation is not the only cause of depression and does not completely explain its pathophysiology because it seems to be a disease with a combination of heterogeneous causes. However, inflammation is an important pathogenic factor that explains a possible mechanism of depression, with the kynurenine (KYN) pathway of tryptophan (TRY) at its center. In particular, the KYN pathway may be more impaired in the inflammation-induced depression that develops after IFN treatment for hepatitis C, cancer, infection, or autoimmune disease, and the mechanism related to the KYN pathway is considered to play a very important role in

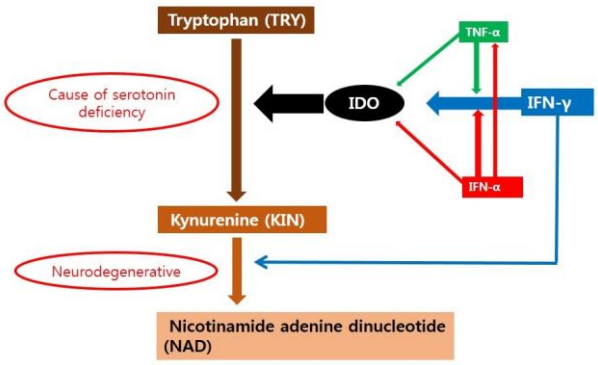
that process. From this perspective, the question, "Can immunopharmacology be applied to the treatment of depression?" can be answered. Although not all immune-modulating medications are effective for depression, they have the potential to be the most important therapy for inflammation-induced depression. Several medications that generally suppress inflammation, such as cyclooxygenase-2 (COX-2) inhibitors and corticotropin-releasing hormone (CRH) antagonists, have already been applied. Applications for the therapeutic efficacy of anti-inflammatory cytokines and anti-cytokine antibodies that can further and more specifically regulate inflammatory cytokines are being prepared, and TNF-α antagonists, such as adalimumab, etanercept, and infliximab, which have already been used as therapeutic agents for rheumatic diseases, are currently being tested in clinical trials for depressed patients. Medications must be developed that can modulate the KYN pathway. To do this, we need to find clear evidence regarding the immune-KYN pathway and to develop theory, based on numerous experiments. Studies of the KYN pathway and depression should address the limitations of the current monoamine-serotonin and cytokine hypothesis theories and are likely to make important contributions to the treatment of inflammation-induced depression.

Figure 1. The tryptophan breakdown metabolic pathway in immune challenges.



The black arrows show metabolic processes. The enzymes that are activated by inflammation and the metabolites that are increased by inflammation are labeled in red. The enzymes that are attenuated by inflammation and the metabolites that are decreased by inflammation are labeled in blue. The red arrows show the stimulant effects in the inflammatory state. The blue arrows show the negative effects or inhibition in the inflammatory state. The thicknesses of the arrows indicate the degrees or weights of the actions or reactions. The green arrows show the vicious cycle sustaining the serotonin deficiency. IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; NMDA R: N-methyl-D-aspartate receptor; α7nAchR: alpha-7-nicotine acetylcholine receptor.

Figure 2. The mechanisms for development of inflammation-induced depression in patients undergoing IFN-α therapy.



IFN-α is much weaker than IFN-γ with respect to IDO activation, but it has the effect of stimulating the production of other pro-inflammatory cytokines, such as IFN-γ and TNF-α. The thicknesses of the arrows indicate the degrees or weights of the actions or reactions. IDO: indoleamine 2,3-dioxygenase; INF: interferon; TNF: tumor necrosis factor.

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Highlights

- Inflammation is an important pathogenic factor that explains a possible mechanism of depression, with the kynurenine(KYN) pathway of tryptophan at its center.
- Greater impairment seems to exist in the KYN pathway in inflammation-induced depression related to immunotherapy, autoimmune disease, and infection.
- Although not all immune-modulating medications are effective for depression, this type has the potential to be the most important therapy for inflammation-induced depression.