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REVIEW ARTICLE

Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression

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Abstract: The autonomic nervous system is one of the major neural pathways activated by stress. In situations that are often associated with chronic stress, such as major depressive disorder, the sympathetic nervous system can be continuously activated without the normal counteraction of the parasympathetic nervous system. As a result, the immune system can be activated with increased levels of pro-inflammatory cytokines. These inflammatory conditions have been repeatedly observed in depression. In the search for the mechanism by which the immune system might contribute to depression, the enhanced activity of indoleamine 2,3-dioxygenase by pro-inflammatory cytokines has been suggested to play an important role. Indoleamine 2,3-dioxygenase is the first enzyme in the kynurenine pathway that converts tryptophan to kynurenine. Elevated activity of this enzyme can cause imbalances in downstream kynurenine metabolites. This imbalance can induce neurotoxic changes in the brain and create a vulnerable glial-neuronal network, which may render the brain susceptible to depression. This review focuses on the interaction between stress, the autonomic nervous system and the immune system which can cause imbalances in the kynurenine pathway, which may ultimately lead to major depressive disorder.

Keywords: Major depressive disorder, stress, autonomic nervous system, immune system, kynurenine pathway.

INTRODUCTION

Major depressive disorder (MDD) is a chronic illness which results in functional impairment. It is characterized by frequent relapses, incomplete recovery and residual symptoms [1]. MDD is projected to become the leading cause of disease burden worldwide by 2030 [2]. As illnesses such as heart disease, type 2 diabetes, autoimmune diseases and cancer, are often associated with depression [3], various possibilities have been posited to explain the link between such illnesses and depression. The disruption of the immune system is viewed as the most plausible explanation [1]. For the past few decades, the immune system has been repeatedly associated with depression in numerous ways [4-7]. The inflammatory response system has been shown to be activated in MDD, but the levels of different inflammatory markers vary across studies [8]. Speculations have been made to explain how the immune system is activated in depression, with stress and its effects on the body receiving much of the attention.

Stress is defined as a state of threatened homeostasis following exposure to extrinsic or intrinsic adverse forces [9]. Acute stress refers to stress that occurs for minutes or hours, whereas chronic stress persists for days, weeks, or months [10]. The major pathways activated by stressors are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) [11]. Stress has repeatedly been associated with depression, and is reported to precipitate depressive episodes and to influence the severity, duration and natural course of the disorder [12]. Acute and chronic stressors have also been reported to affect the immune system, and an increase in various inflammatory markers has been reported in states of acute stress [13] and chronic stress [14]. A potential interaction between chronic stress and inflammatory cytokine responses to acute stress has also been reported [15].

In the search for the mechanism by which the immune system might contribute to depression, decreased serum tryptophan concentrations were noted in depressed patients who had inflammatory disorders, or who had received cytokine immunotherapy [16, 17]. Tryptophan functions as a biochemical precursor for serotonin, which in turn has been strongly implicated in the pathogenesis of depression [18]. In 1969, Lapin and Oxenkrug proposed that in depression the metabolism of tryptophan is shunted away from serotonin production towards kynurenine production, resulting in tryptophan depletion [19]. Cytokines produced in inflammatory states were considered to induce tryptophan depletion by enhancing the activity of indoleamine 2,3-dioxygenase (IDO), the first enzyme in the kynurenine (KYN) pathway that converts tryptophan to KYN [16, 20]. Based on these findings, the "neurodegeneration hypothesis of depression" was proposed [21] which hypothesized that imbalances in downstream KYN metabolites induce neurotoxic changes that create a vulnerable glial-neuronal

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network, which may contribute to the development of depression.

This review focuses on the interaction between stress, the ANS and the immune system, which can cause imbalances in the KYN pathway that may ultimately lead to depression. Although stress initially activates both the ANS and the HPA axis, this review will focus on the role of the ANS, which has received much less attention than the HPA axis [22].

STRESS, THE AUTONOMIC NERVOUS SYSTEM AND THE IMMUNE SYSTEM

Brief laboratory stressors, such as mental arithmetic and public speaking tasks, have been reported to induce increases in natural killer cell activity [23]. These increases were potentiated in individuals who were more cardiovascularly reactive to stress [24]. This was interpreted as individuals who showed the greatest sympathetic nervous system (SNS) and endocrine response to brief psychological stressors, also showed increased immune system alterations. Thus, the effect of stress on the neuroendocrine system and how this effect influences the immune system, has become a subject of interest in recent years [25].

Stress, the Sympathetic Nervous System and the Parasympathetic Nervous System

The ANS has two divisions, the SNS and the parasympathetic nervous system (PNS). In response to stressors, the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine vasopressin. From the paraventricular nucleus of the hypothalamus, CRH-containing neurons have projections to noradrenergic centers in the brainstem and spinal cord. The locus coeruleus of the brainstem sends direct projections to the sympathetic preganglionic neurons in the spinal cord and to the parasympathetic preganglionic neurons in the brainstem and the spinal cord [26]. In general, the locus coeruleus increases sympathetic activity through the activation of α1-adrenoceptors on preganglionic sympathetic neurons [27] and reduces parasympathetic activity through the activation of α2-adrenoceptors on preganglionic parasympathetic neurons [28]. The activation of the SNS in turn stimulates the release of CRH by the hypothalamus, creating a positive bidirectional feedback loop [29].

The principal neurotransmitters of the ANS are norepinephrine (NE), epinephrine (E) and acetylcholine (ACh) [30]. The sympathetic system controls catecholamine biosynthesis and secretion from the adrenal medulla, which is innervated by preganglionic sympathetic fibers of the splanchnic nerve [31]. Medullary cells mainly release E, and to a lesser extent NE, into the blood rather quickly when stimulated by the SNS in response to stressors [31]. Therefore, the principal end products of the SNS are NE and E. The PNS mainly uses ACh as its neurotransmitter [32]. Under normal conditions, the PNS is activated when the stressful situation is alleviated because the SNS and the PNS are highly coordinated to maintain physiological homeostasis [33]. However, in abnormal conditions in which the stressful situations persist, the SNS continues to be activated without the normal counteraction of the PNS. As a result, in chronically stressful situations, peripheral levels of catecholamine can increase and levels of acetylcholine can decrease [9] Fig. (**1**).

The Autonomic Nervous System and the Immune System

Inflammatory responses are characterized by a complex interaction between pro- and anti-inflammatory cytokines [34]. E and NE modulate the release of cytokines and inflammation through α- and β-adrenoceptors on immune cells [35]. Results of *in vitro* and *in vivo* studies have suggested that NE enhances tumor necrosis factor (TNF) production [36, 37]. Both catecholamines have been reported to stimulate interleukin (IL)-6 release by immune cells and other peripheral cells [38]. NE has also been shown to augment macrophage phagocytosis and tumoricidal activity [39]. In contrast, ACh has been reported to dose-dependently inhibit the release of TNF, along with other pro-inflammatory cytokines such as IL-1, IL-6, and IL-18 [40]. However, the production of IL-10, which is an anti-inflammatory cytokine, was reported to be unaffected by ACh. The inhibition of acetyl-cholinesterase activity, which increases ACh levels in the central nervous system, resulted in the suppression of the immune response, indicating that ACh has an immunoinhibitory role in the brain [41]. When stressful situations are prolonged, adrenergic agents can increase and ACh can decrease, because of the continuous activation of the SNS and the lack of counter activation of the PNS. As a result, pro-inflammatory cytokines, such as TNF, IL-1, and IL-6, can increase in prolonged stressful situations such as depression.

THE IMMUNE SYSTEM AND DEPRESSION

Sickness behavior, which refers to the depression-like symptoms that accompany the response to infection, was reported to be induced by cytokines such as IL-1 [42]. Sickness behavior due to peripheral immune activation was also reported to be reversed by the administration of the IL-1 receptor antagonist, which suggested a link between immune activation and depressive-like behavior. Thereafter, theories on how immune activation and depression were related were proposed. In the macrophage theory of depression, excessive secretion of macrophage monokines, such as IL-1, was proposed as the cause of depression [43]. Subsequent studies on depression in cancer patients receiving cytokine therapy supported the assumption that immune activation can cause depression [44-46]. Improvement in depressive symptoms in patients with moderate to severe psoriasis receiving TNF antagonist treatment was also reported, with improvement being independent of the effect of the treatment on joint pain [47]. Studies of medically healthy subjects reported an association between depressed mood and increased production of pro-inflammatory cytokines such as TNF, IL-1, and IL-6 [48-50]. TNF and IL-6 have also been reported to be elevated in MDD patients [51], and meta-analyses have confirmed IL-6 levels to be elevated in depressed patients [8]. Anti-inflammatory cytokines, such as IL-10, have been reported to be reduced in MDD patients [52].

Based on the evidence stated above, it is clear that a relationship exists between inflammation and depression. However, it is not yet evident how states of chronic

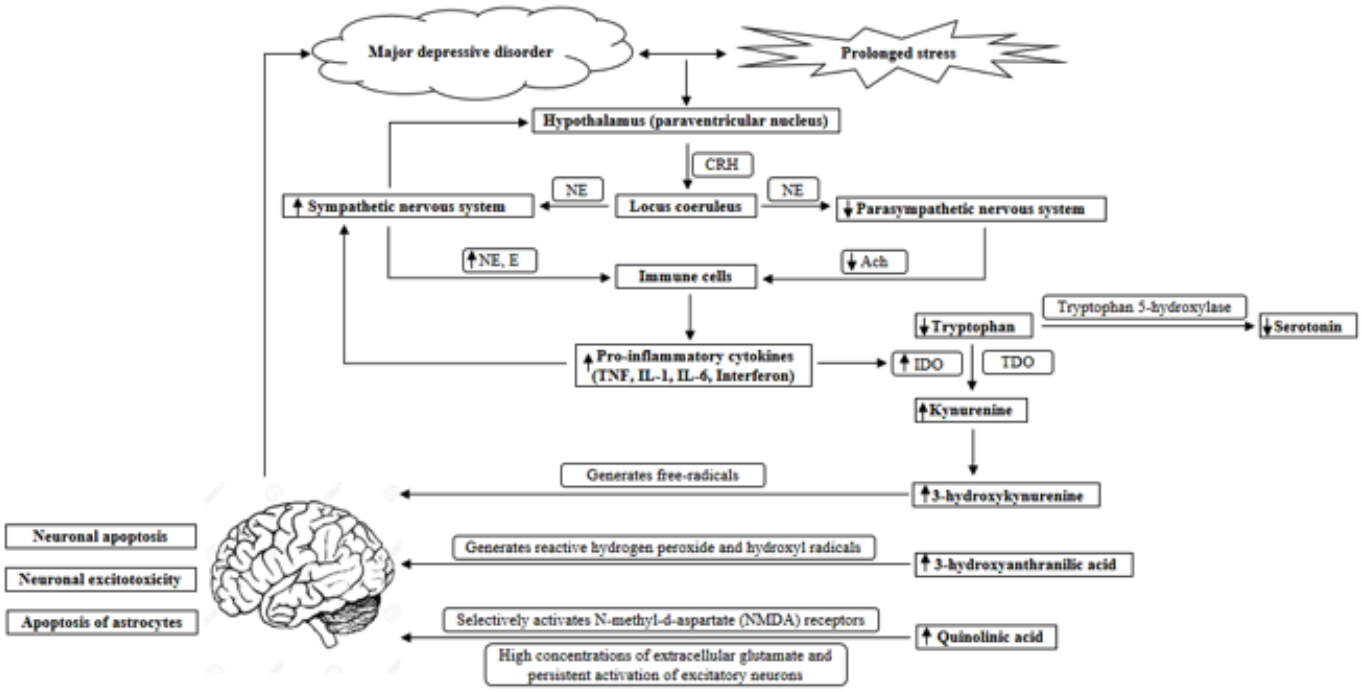

Fig. (1). The interaction between stress, the autonomic nervous system, the immune system and the kynurenine pathway in the etiology of depression. The hypothalamus secretes CRH in response to stress, and from the paraventricular nucleus of the hypothalamus, CRH-containing neurons have projections to the locus coeruleus. The locus coeruleus sends direct projections to the sympathetic and parasympathetic preganglionic neurons, increasing sympathetic activity and decreasing parasympathetic activity through the activation of adrenoceptors. In turn, the activation of the sympathetic nervous system stimulates the release of CRH. When stress is prolonged, as in major depressive disorder, the sympathetic nervous system continues to be activated, with a lack of parasympathetic counter activity. As a result, NE and E levels are increased and ACh levels are decreased, which lead to an increased release of pro-inflammatory cytokines from immune cells. Pro-inflammatory cytokines, such as TNF, IL-1, IL-6 and interferons can induce IDO activity, which increases the KYN/tryptophan ratio. As a result, downstream metabolites, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid are increased, which all have neurotoxic effects on the brain. 3-hydroxykynurenine generates free-radicals and causes neuronal apoptosis. 3-hydroxyanthranilic acid generates highly reactive hydrogen peroxide and hydroxyl radicals. Quinolinic acid selectively activates N-methyl-d-aspartate (NMDA) receptors, and high concentrations of extracellular glutamate and persistent activation of excitatory neurons cause excitotoxicity. Therefore, the accumulation of quinolinic acid can result in neuronal excitotoxicity and the selective apoptosis of astrocytes. This can ultimately lead to neurodegenerative changes, which may render the brain susceptible to depression.
CRH = corticotropin-releasing hormone; NE = norepinephrine; E = epinephrine; ACh = acetylcholine; TNF = tumor necrosis factor; IL-1 = interleukin-1; IL-6 = interleukin-6; IDO = indoleamine 2,3-dioxygenase; KYN = kynurenine.

inflammation may lead to depression. This could be explained by increased tryptophan degradation due to the enhanced IDO activity of the KYN pathway in inflammatory conditions.

The Tryptophan Breakdown Metabolic Pathway in Normal Conditions

When two atoms of oxygen are inserted into tryptophan, N-formylkynurenine is formed, which is the first step in the KYN pathway. Approximately only 1% of dietary tryptophan is converted to serotonin, the remaining 99% of tryptophan is metabolized through the KYN pathway [53]. Tryptophan is catalyzed into KYN by three different enzymes, tryptophan 2,3-dioxygenase (TDO), IDO1 and IDO2. However, the biological function of IDO2 is still unclear and needs clarification [54]. TDO is highly substrate-specific and dioxygenates only L- tryptophan and some tryptophan derivatives. The expression of TDO is normally restricted to mammalian liver cells where it is believed to regulate systemic tryptophan concentrations [55]. In normal conditions, the activity of TDO is generally stable and is mainly controlled by the tryptophan level itself [56]. IDO activity in nonpathological conditions is minimal [53]. The KYN pathway is initiated by the oxidative cleavage of the indole-ring of tryptophan by TDO and IDO, forming N-formylkynurenine [57]. KYN is then synthesized and metabolized through one of the three mechanisms. Kynurenine amino-transferase enzymes deaminate KYN, resulting in kynurenic acid. KYN is also degraded by kynureninase resulting in anthranilic acid. Hydroxylation of KYN by kynurenine monooxygenase produces 3-hydroxykynurenine. This 3-hydroxykynurenine is in turn converted into 3-hydroxyanthranilic acid by kynureninase, and then oxidized by 3-hydroxyanthranilic acid oxidase into 2-amino-3-carboxymuconic 6-semialdehyde, which reassembles to form quinolinic acid. Quinolinate phosphoribosyl transferase transaminates quinolinic acid to nicotinic acid and ultimately to NAD+. 2-amino-3-carboxymuconic 6-semialdehyde can also be metabolized and produces picolinic acid through the activity of 2-amino-3-carboxymuconic-6-semialdehyde decarboxylase [54, 56, 57].

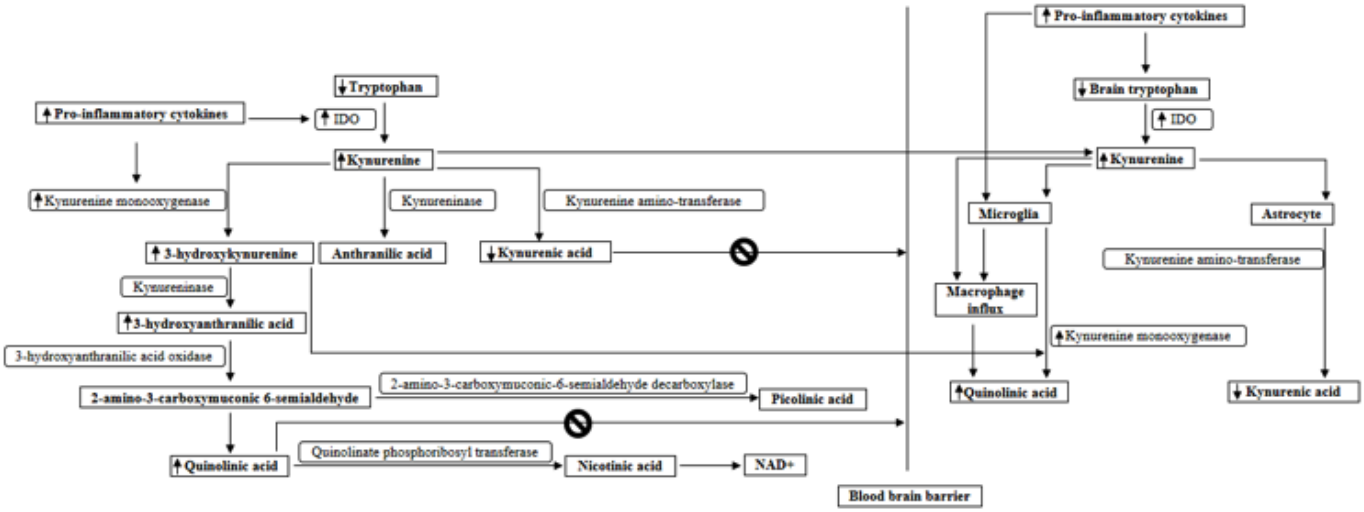

Fig. (2). IDO and kynurenine monooxygenase activity are enhanced by pro-inflammatory cytokines, and as a result the balance between the formation of 3-hydroxykynurenine and of kynurenic acid is shifted to the side of 3-hydroxykynurenine, which forms 3-hydroxyanthranilic acid and finally quinolinic acid. As KYN synthesized in the periphery can also penetrate the brain, KYN pathway metabolism in the brain is also initiated by KYN that crosses the blood brain barrier. KYN and 3-hydroxykynurenine easily cross the BBB, whereas quinolinic acid and kynurenic acid crosses the BBB poorly. The 3-hydroxykynurenine arm of the pathway leading to quinolinic acid production takes place in microglia, and kynurenic acid production takes place in astrocytes. The KYN pathway in the microglia can be enhanced in inflammatory conditions, as kynurenine monooxygenase activity is enhanced by pro-inflammatory cytokines. Immune responses can also activate microglia and cause an influx of macrophages into the brain, which causes a significant increase in quinolinic acid synthesis.
IDO = indoleamine 2,3-dioxygenase; KYN = kynurenine.

TDO and IDO1 levels are much lower in the brain than in the periphery [58], and therefore up to 60% of KYN pathway metabolism in the brain is initiated by the brain penetrant KYN synthesized in the periphery [59]. KYN is further degraded in the brain into different metabolites, depending on the cell type in which KYN is produced or transported [60, 61]. The KYN pathway takes place predominantly in microglia and astrocytes in the central nervous system [57], however the KYN metabolism is separated in the brain, as kynurenine monooxygenase is expressed in microglia but not in astrocytes [62], and kynurenine amino-transferase enzymes are expressed in astrocytes but not in microglia [63]. Therefore, the 3-hydroxykynurenine arm of the pathway leading to quinolinic acid production takes place in microglia, and kynurenic acid production takes place in astrocytes. Also, intact neurons can degrade KYN into picolinic acid [64].

The Tryptophan Breakdown Metabolic Pathway in Inflammatory Conditions

IDO1 is expressed in a broad variety of mammalian cells related to immune function, such as activated macrophages and dendritic cells [54]. The first studies comparing the effect of interferons on IDO induction in immunocompetent cells were published by Werner-Felmayer G, *et al*. [65, 66]. The results of these studies demonstrated that induction of IDO is a common feature of interferon-gamma action, and the extent of this induction is influenced by extracellular L-tryptophan concentrations, and IDO is the only enzyme in the formation of 3-hydroxyanthranilic acid from tryptophan which is regulated by interferon-gamma. In states of inflammation and oxidative stress, proinflammatory cytokines, such as TNF [67] and reactive oxygen species, can induce IDO activity in extrahepatic tissues, such as the lung, placenta, kidney, spleen, blood and brain [68, 69]. The extrahepatic tryptophan metabolism then shifts the tryptophan metabolism away from the liver [70], and a large amount of tryptophan degradation takes place in the blood and lymphoid tissues through the KYN pathway [71]. Therefore, activation of IDO1 increases the KYN/tryptophan ratio [72]. Enhanced IDO activity during inflammation is initially a reflex mechanism that suppresses inflammatory reactions [56]. Tryptophan depletion through IDO activation induces a balance between pro-inflammatory T helper 17 cells and anti-inflammatory T-regulatory cells by suppressing effector T-cell activity and expanding T-regulatory cells [73], influencing the pro-inflammatory response [74]. As a result, immune tolerance is achieved and the KYN pathway homeostasis is maintained. However, if inflammatory conditions exist chronically, causing disturbances in the tryptophan metabolism, this may result in excessive tryptophan depletion and an accumulation of downstream metabolites of the KYN pathway.

Since kynurenine monooxygenase activity is enhanced by pro-inflammatory cytokines [68], 3-hydroxykynurenine formation is increased in inflammatory states, compared to kynurenic acid formation. The balance between the formation of 3-hydroxykynurenine and of kynurenic acid is shifted to the side of 3-hydroxykynurenine, which finally forms quinolinic acid [56]. The KYN pathway in the astrocytes and microglia in the brain can be enhanced in inflammatory conditions through the body–brain cross talk of the pro-inflammatory molecules, such as IL-1 [56]. Immune responses can also activate microglia and cause an influx of proinflammatory cytokines and macrophages into the brain [57]. Because macrophages have a much higher

capacity for producing quinolinic acid than microglia, macrophage and cytokine influx can cause significant changes to the levels of KYN metabolites in the CNS [62]. Also, KYN metabolites, such as picolinic acid, activate the inflammatory reaction and further prolong the inflammatory process, which leads to increased quinolinic acid synthesis [75] Fig. (**2**).

Neurotoxic effects of the Kynurenine Pathway Metabolites in Depression

Initial theories on how the immune-mediated activation of the tryptophan degradation pathway was related to depression, suggested that disturbed metabolism of tryptophan affects the biosynthesis of serotonin, and this appeared to be associated with an increased susceptibility for depression. Also, it was suggested that activation of IDO could represent an important link between the immunological network and the pathogenesis of depression [76]. Studies on tryptophan depletion in healthy controls reported that lowering plasma tryptophan accompanied a decline in central serotonin [77]. Tryptophan depletion was reported to have mood-lowering effects in subgroups of recovered depressed patients and in vulnerable healthy subjects with a family history of depression [78]. However, subsequent studies reported that brain tryptophan did not decrease in inflammatory conditions, but rather it increased, accompanied by an increase in brain serotonin turnover [79]. The brain seemed to compensate for the decrease in circulating tryptophan induced by acute or chronic inflammation by increasing brain tryptophan and stimulating brain serotonin metabolism [80]. Also, a study on interferon α-treated patients reported stable cerebrospinal fluid tryptophan levels, despite the fact that the patients had decreased blood tryptophan levels [81]. Therefore due to the numerous conflicting results stated above, the hypothesis that decreased serotoninergic neurotransmission due to a decreased amount of tryptophan being responsible for inflammation-induced depression, was no longer tenable [64]. Thereafter, theories were suggested on how the immune-mediated activation of the tryptophan degradation pathway plays a role in depression. As KYN pathway metabolites contribute directly to neuroprotective and neurodegenerative changes in the brain through the network with several neurotransmitter systems, an imbalanced KYN pathway that increases neurotoxic KYN metabolites, which in turn induces an impaired glial–neuronal network, was viewed as the most plausible explanation [56].

The increase in tryptophan degradation in chronic inflammatory states results in extra amounts of peripheral KYN, which cross the BBB and become available for the downstream KYN pathway in the brain [56]. KYN pathway metabolites, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid, are increased in inflammatory states and are all neurotoxic [57]. Also, KYN and 3-hydroxykynurenine easily cross the BBB, whereas quinolinic acid crosses the BBB poorly [82]. 3-hydroxykynurenine generates free-radicals by oxidizing interacting molecules [83]. It has been shown to induce reduced viability, shrunken somata and reduced neuritic outgrowths in cultured striatal and cortical neurons, causing neuronal apoptosis [84]. 3-hydroxyanthranilic acid also auto-oxidizes and generates highly reactive hydrogen peroxide and hydroxyl radicals [85]. Quinolinic acid selectively activates N-methyl-d-aspartate (NMDA) receptors [86], stimulates neuronal release of glutamate, inhibits astroglial reuptake of glutamate [87] and reduces the activity of glutamine synthetase which facilitates glutamine production from glutamate and ammonia [88]. In turn, high concentrations of extracellular glutamate and persistent activation of excitatory neurons cause excitotoxicity [89]. Therefore, the accumulation of quinolinic acid can result in neuronal excitotoxicity and the selective apoptosis of astrocytes [90]. On the other hand, kynurenic acid, which is decreased in inflammatory states, scavenges free radicals, such as hydroxyls and superoxide anions, and possesses antioxidant properties [91]. Kynurenic acid can act as non-selective antagonists of NMDA receptors at high concentrations [92]. Through this modulation of glutamate signaling and antioxidant activity, kynurenic acid counteracts neurotoxicity [57]. However peripheral kynurenic acid crosses the BBB poorly [82]. If an imbalance between neurotoxic and neuroprotective KYN metabolites chronically persists, damage to the glial–neuronal network might be progressive, priming the brain to be vulnerable to pathologic conditions such as depression [56].

Previous studies have reported an imbalance between the neuroprotective and the neurotoxic KYN pathways in MDD. The mean plasma kynurenic acid values and the mean kynurenic acid/KYN ratio were reported to be significantly lower in MDD patients compared to healthy controls [93]. Elevated KYN/tryptophan ratios and a positive relationship between MDD severity and 3-hydroxyanthranilic acid/KYN ratio were observed in adolescent MDD patients with melancholic features compared to healthy controls [94]. These results indicated a shift in the KYN pathway, more to the arm of 3-hydroxyanthranilic acid, where other neurotoxic metabolites, such as 3-hydroxy-kynurenine and quinolinic acid, can be formed [56]. In animal studies, cytokines, such as TNF, were elevated in mice that showed depressive-like behaviors after bacille Calmette-Guérin (BCG) injections, and the enzyme 3-hydroxyanthranilic acid oxidase was also up-regulated [95]. The activation of 3-hydroxyanthranilic acid oxidase enzyme would enhance the degradation of 3-hydroxyanthranilic acid, which would further enhance the formation of quinolinic acid. Increased density of quinolinic acid positive cells of the anterior cingulate cortex, a brain area which has repeatedly been implicated in the pathology of MDD [96], has been reported in acutely depressed patients who have committed suicide [97]. Increased excitotoxic metabolites can have detrimental effects on the brain, such as decreases in neuronal and glial sizes and densities, which have previously been reported in studies on MDD [98].

CONCLUSIONS

Given the evidence stated above, it is likely that stress increases the activity of the SNS and decreases the activity of the PNS, which increases the levels of E and NE, and decreases the level of ACh. This in turn can increase the level of pro-inflammatory cytokines, such as TNF, IL-1,

IL-6, and interferons and decrease the level of anti-inflammatory cytokines, such as IL-10, resulting in a state of inflammation. Inflammatory conditions can induce IDO activity, increase the KYN/tryptophan ratio and cause a shift in the KYN pathway, resulting in an imbalance between neuroprotective and neurotoxic KYN metabolites. This can ultimately lead to neurodegenerative changes of the brain, which may render the brain susceptible to depression, as summarized in Fig. (**1**). Recent reviews have reported the associations among the KYN pathway, inflammatory cytokines and neurotoxicity of KYN pathway metabolites in depression [99, 100]. Furthermore, we have also considered the role of stress and the autonomic nervous system along with inflammatory cytokines and the KYN pathway in our review, when discussing the pathogenesis of depression.

In accordance with our current understanding of how depression represents a state of inflammation, previous studies have attempted to investigate whether anti-inflammatory drugs could have treatment effects on MDD. Several human and animal studies have suggested that certain anti-inflammatory drugs might play an important adjunctive role in the treatment of major depression [101]. As we consider inflammatory conditions to be caused by an over-driven SNS together with an under-driven PNS induced by stress, treatments that increase the parasympathetic tone and hence strengthen the cholinergic anti-inflammatory pathway [102] may be useful in treating MDD. This may explain why methods that increase parasympathetic tone, such as vagus nerve stimulation, have been suggested to be effective in treating depression [103].

Further research on the use of KYN metabolism related markers in the early diagnosis of depression, and novel therapeutic methods involving the normalization of the ANS, immune system and KYN pathway, will help to develop effective ways to detect and treat MDD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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