The tryptophan catabolite or kynurenine pathway's role in major depression

Minireview

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Abstract

Kynurenine or tryptophan catabolite (TRYCAT) pathway contributes to the pathophysiology of major depression disorder (MDD) and major depressive episodes (MDE) in bipolar disorder and suicidal behaviors. The consequences of the overactivation of this pathway large reduced tryptophan (TRP) levels in peripheral blood and the CNS and increased levels of neurotoxic TRYCATs including kynurenine (KYN), 3-hydroxy kynurenine (3HK), quinolinic acid (QA), xanthurenic acid (XA), and picolinic acid (PA). However, other TRYCATs are protective, such as kynurenic acid (KA) and anthranilic acid (AA). Inflammation and cell-mediated immune activation along with oxidative and nitrosative stress (O&NS) may stimulate the first and rate-limiting enzyme of this pathway, namely indoleamine-2,3-dioxygenase (IDO). Therefore, during depression, balancing neuroprotective versus neurotoxic TRYCATs and balancing activation of the immune response system (IRS) versus the compensatory immune response system is crucial for achieving better treatment outcomes. Furthermore, targeting the causes of TRYCAT pathway activation (immune activation and O&NS) is probably the most effective strategy to treat depression. In the present review, we aim to provide a comprehensive explanation of the impact of TRYCATs in terms of pathophysiology and treatment of MDD and MDE.

Keywords: TRYCATs, MDD, MDE, Suicidal behavior, Kynurenine pathway.

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1. Introduction

First, we would like to congratulate Messaoud et al. for their valuable article published in Current Topics in Medicinal Chemistry [1]. The results show that patients with MDD and suicidal behaviors had elevated levels of KYN, KYN/TRP ratio, and proinflammatory cytokines (PIC), namely interleukin-1 (IL)-1 and IL-12 as well as a diminished TRP levels when compared with non-suicidal MDD patients. Besides, there were no significant differences between non-suicidal and suicidal MDD patients in cortisol, IL-6, and IL-20. Hence, the authors concluded that the TRYCAT pathway is implicated in the pathophysiology of MDD and suicidal behaviors [2-4].

There is now evidence that both MDD and a MDE in bipolar disorder are characterized by a) activation of the immune-inflammatory response system (IRS) as indicated by increased macrophage M1 and T helper (Th)1 cytokines, such as IL-1β, IL-6, IL-8, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and chemokines b) activation of the compensatory immune-regulatory reflex system (CIRS) as shown by elevated Th2 and T regulatory (Treg) cytokines or their receptors, namely IL-4, IL-10, sIL-1RA, sIL-2R and TNF-α receptors along with other CIRS markers, including increased positive acute phase proteins (APPs), e.g. haptoglobin, hemopexin, α1-acid glycoprotein, α1-antitrypsin and ceruloplasmin [5]. There is also evidence that suicidal ideation and attempts are characterized by activated IRS pathways [6].

2. The impact of immune activation on Tryptophan.

Already in the 1990s it was observed that immune biomarkers such as IL-6 and haptoglobin were inversely correlated with plasma levels of TRP and the TRP/ competing

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amino acid (CCA) ratio, indicating that lowered TRP in mood disorders is an index of an ongoing IRS response [4]. The depletion of TRP was explained by increasing its catabolism due to stimulation of the first and rate-limiting enzyme, namely IDO, which is induced by cell-mediated immune pathways [4]. Furthermore, early research also showed increased serum and urinary concentrations of neopterin in patients with depression and a significant inverse association between plasma TRP and neopterin [7]. Neopterin is a sensitive marker of CMI and inflammation and elevated levels are observed in several autoimmune and inflammatory disorders, e.g. rheumatoid arthritis, and Crohn's disease. IFN-γ not only stimulates IDO but also guanosine-5-cyclohydrolase I thereby degrading GTP and producing neopterin. Both IFN-γ-induced pathways may explain the inverse association between lowered TRP and increased neopterin in patients with mood disorders [7].

Lowered TRP levels in association with immune-inflammatory biomarkers were also established in the prepartum period and the early puerperium [8]. Plasma TRP and the TRP/CAA ratio were significantly and inversely associated with IRS activation, as assessed with increased serum levels of IL-6 and IL-1 receptors antagonist (IL-1RA), suggesting that elevated PIC levels lead to TRP catabolism due to IDO enzyme activation. Nonetheless, no significant correlation between low TRP and TRP/CAA and post-natal depressive and anxiety symptoms was detected, although the latter were associated with IRS activation [8].

3. The role of cytokines in triggering TRYCAT pathway and hence depressive symptoms

The first mechanistic paper showing that cytokines (IFN-α administration) may cause depressive symptoms by inducing the cytokine network in association with depletion

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of plasma TRP and increased production of KYN was reported by Maes' laboratories [4, 9-11]. Interestingly, the IFN-α induced increases in KYN were more significantly associated with the onset of depressive symptoms than the lowering of plasma TRP. Moreover, the onset of depressive symptoms following IFN-α administration was associated with an increase in the KYN/KA ratio, which reflects increased neurotoxicity (KYN) versus neuroprotection (KA) [4, 12]. Such findings lead these authors to formulate the new theory that increased neurotoxicity rather than changes in the serotonin system may explain the onset of inflammation-induced mood disorders [11].

Increased TRYCATs-induced neurotoxicity is the result of cytokine-induced IDO activity and the overproduction of neurotoxic TRYCATs, including KYN, 3HK , PA, XA and QA. Thus, following immune injuries two types of balance appear to be important: a) IRS versus CIRS cytokines/immune products and b) neurotoxic (KYN, 3HK, PA, XA, QA) versus neuroprotective KA and AA TRYCATs [3]. When these balances are disrupted, the IRS and neurotoxic branch of the TRYCAT pathway will be overactivated with a shift towards increased immune neurotoxicity leading to neurodegenerative processes in multiple brain circuits [11, 13].

Depression shows a strong comorbidity with somatization (multi-somatoform illness defined by medically unexplained symptoms and a two-year or longer history of somatization). Lowered TRP and KA levels but increased KYN/TRP (IDO proxy) and KYN/KA (neurotoxic/neuroprotective ratio) were observed in patients with comorbid somatization and depression when compared to healthy controls and patients with depression only [14]. Thus, activation of the TRYCAT pathway with lowered TRP availability to the brain (and thus probably lowered serotonin synthesis in the central

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nervous system (CNS) and increased TRYCATs neurotoxicity may be implicated in the onset of somatization and depression comorbid with somatization. As such, somatization rather than depression per se may be associated with TRYCAT pathway activation.

A significant number of patients with schizophrenia also suffer from affective symptoms and depression and anxiety due to schizophrenia are associated with increased IgA responses directed against TRYCATs, including 3HK, PA and XA relative to KA and AA. As such, affective symptoms due to schizophrenia are also accompanied by an increased neurotoxic ratio [15].

Nevertheless, induction of the TRYCAT pathway in depression is probably not only a consequence of IRS activation but also of increased oxidative stress and increased LPS levels following increased translocation of Gram-negative bacteria [16]. First, there is evidence of increased reactive oxygen (ROS) and nitrogen (RNS) species in depression and suicidal behaviors with increased superoxide, nitric oxide, peroxynitrite, and hydrogen peroxide production [17-19]. Such changes not only lead to decreased neurogenesis, neurodegenerative processes, and reduction in brain volume but also to increased staging characteristics as indicated by an increased reoccurrence of illness index (ROI) and suicidal behaviors [19-21]. Second, increased gut permeability or leaky gut may cause increased bacterial translocation and thus increased LPS load in the peripheral blood of patients with depression [16]. This toxin is recognized by the Toll-Like Receptor (TLR)4 complex located on peripheral blood mononuclear cells (PBMCs), neurons, microglia, and astrocytes and triggers an immune and O&NS stress response through activation of nuclear factor B (NF-κB) and mitogen-activated protein kinases (MAPK). As such, IDO activation

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in depression may be the consequence of intertwined associations among IRS and O&NS activation and increased bacterial translocation.

4. Functions of TRYCATs

Activation of IDO enzyme with lowered TRP levels and increased levels of TRYCATs is part of an adaptive immune response because a) reduced TRP has antimicrobial properties and anti-inflammatory properties through TRP starvation; and b) some TRYCATs (KYN, KA, XA, QA) have anti-inflammatory properties by reducing the IFN-γ/IL-10 production ratio [22]. Moreover, KYN induces Treg development and TRYCATs such as 3HA have strong anti-inflammatory effects. Some TRYCATs have also antioxidant effects, for example 3HK and 3HA are more potent than α- tocopherol as radical scavengers [3]. Also, XA has similar antioxidant activity as compared with butylated hydroxytoluene (BHT), while KA has less antioxidant activity than BHT [23]. Moreover, XA may display neuroprotective properties by attenuating vesicular glutamate transport (VGLUT), synaptic transmission via the NMDAR receptor, and excitatory postsynaptic potentials (review: Kanchanatawan, et al. [24]) It should be added that KA has neuroprotective effects by inhibiting NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate glutamate ionotropic receptors and attenuating glutamate release resulting from inhibition of alpha 7 nicotinic acetylcholine receptor (α7nAChr) [25]. Also, AA has neuroprotective effects by inhibiting the production of neurotoxic TRYCATs, such as PA and QA from 3HA [26]. All in all, the activation of the TRYCAT pathway has intrinsic protective effects by ROS scavenging and negative immune-regulatory and neuroprotective effects [22].

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Nevertheless, some TRYCATs when overproduced have also neurotoxic effects. First, most TRYCATs have beside antioxidant also pro-oxidant effects, including increased oxidative stress due to 3HA [27, 28], increased ROS produced by 3HK [29], increased hydrogen peroxide and superoxide production by both 3HK and 3HA [30], and ROS generated by QA [31]. In addition, free radicals formed by 3HK and 3HA may cause oxidative damage to the cells [32,33] and ROS generated by QA may cause lipid peroxidation and consequent neurotoxicity [31]. Second, QA may cause apoptosis and hippocampal atrophy by overactivation of hippocampal N-methyl-D-aspartate (NMDA) receptors [22]. XA has also neurotoxic effects by inducing apoptosis, mitochondrial dysfunctions, and intracellular hypercalcemia due to overstimulation of cationic channels resulting in excited neural networks [24]. This explains that increased XA levels may lead to significant neuronal injury, impaired transmission of glutamate, and may impede presynaptic transmission triggered by stimulating NMDArs [24]. PA may enhance immune-inflammatory responses and by reducing KA and AA attenuate neuroprotection (review: Kanchanatawan et al [24]). Third, some TRYCATs, particularly KYN, are depressogenic and anxiogenic [3], although KA may have antidepressant effects [34]. Therefore, TRYCATs have different functions, including immunoregulatory versus proinflammatory, anti- versus pro-oxidant, and neuroprotective versus neurotoxic effects. As a result, TRYCAT pathway activation in depression has intrinsic antioxidant and negative immune-regulatory effects and depending on the production rates of QA, KYN, 3HK, PA, and XA may have detrimental effects. The latter effects may then aggravate the immune and oxidative neurotoxicity as a consequence of M1 and Th1 cytokines, lipid peroxidation, protein oxidation, hypernitrosylation, and autoimmune responses [6, 35].

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5. Neurotoxic indices

Apart from data on the KA/KYN ratio (which reflect one aspect of neuroprotection versus neurotoxicity), there is no clear information about other neurotoxicity indices, including composite scores of the most important neurotoxic TRYCATs (KYN + 3HK + XA + PA + QA) and the ratio of generally more neurotoxic / neuroprotective TRYCATs (KYN + 3HK+ XA + PA + QA / AA+KA). Likewise, apart from some data on the KYN/TRP which is a proxy for IDO activity, other ratios (computed as composite scores) such as KA/KYN, and KA/(KYN+TRP) (both assessing KAT activity) and 3HK/KYN or 3HK/KYN+TRP (both assessing KMO activity) are missing [36].

6. Important aspects in considering peripheral TRYCATs

When interpreting peripheral TRYCATs data there are, however, several caveats. There is a substantial relationship between either free or total TRP in peripheral blood and TRP and, consequently, 5-HT synthesis in the CNS [37, 38]. Nevertheless, TRP reaches the brain via the large neutral amino acid transporter-1 (LAT-1) and other amino acids (CAAs) may compete for transport via the same transporter, the most important CAA being leucine, isoleucine, valine, tyrosine, and phenylalanine. Therefore, some authors propose to compute the TRP/CAA ratio in peripheral blood as an index of TRP availability to the brain [39]. Since peripheral blood levels of TRP are strongly bound to albumin any changes in the latter may be accompanied by changes in TRP availability to the brain. This is important because albumin is a negative APP which is downregulated during an immune-inflammatory response including in depression [40]. Furthermore, to cross the BBB, TRP and KYN utilize the same transporter [41]. LAT-1 transports KYN and 3HK to the brain at a high rate, while AA is passively transported at a considerable rate, and 3HA, KA, and

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QA have significantly lower rates of passive diffusion [42]. Kita et al. (2002) discovered that peripheral blood concentrations of KYN and QA partly determine the CNS concentrations of KYN and QA [41]. The TRYCAT concentrations in the peripheral circulation are responsible for around 60% of the KYN concentrations in the CNS [43]. As a consequence, increased TRYCAT production and TRP depletion due to peripheral immune-inflammatory processes influence CNS TRYCAT concentrations and production [41, 44].

Recently, we detected a significant dissociation between the relationships between schizophrenia and TRYCATs levels in the CNS, plasma and serum [36]. The results in the CNS indicate an increase in KYN and KA, and IDO and KAT activities, and a decrease in KMO activity in schizophrenia (as assessed with the composite ratios discussed above). In contrast, in plasma no such changes or even contradictory changes were established, while in serum, only a modest increase in IDO activity could be found [36]. Even more frustrating is the finding that the association between KYN and schizophrenia was significantly different between the CNS (significantly increased), serum (not significant), and plasma (significantly decreased). Further studies should examine these differences in affective disorders.

7. Future treatments

Some authors advocate that targeting IDO may be a new drug target to treat clinical depression by lowering the production of neurotoxic TRYCATs [45,46]. However, given that the major functions of this pathway comprise antioxidant and negative immune regulatory activities, inhibiting IDO activity is probably not a viable strategy [3]. First, it is more adequate to block the activated neuro-immune and O&NS pathways, and

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hypernitrosylation and improve the depleted antioxidant defenses because these pathways are directly associated with staging and the phenome of affective disorders [5]. Second, another approach would be to increase KA activity by administration of specific diets [47], KA supplements and a ketogenic diet, which may increase KA levels [48], or KA analogs [49]. However, KA itself has limited ability to cross the BBB [42] and treatment with KA enhancing strategies is also not evident because KA may interact with several receptors in the CNS, and influence various neurotransmitter systems [50]. Hopefully, the new precision psychiatry approach will eventually reveal the best drug targets in the TRYCAT pathway to treat specific endophenotypes of depression.

Conclusion

The robust evidence concerning high levels of TRYCATs in patients with MDD, MDE besides suicidal behavior frankly confirm the implication of these TRYCATs in the pathophysiology of the mentioned conditions although TRYCATs have some protective functions. Thus, they future treatment should target the normalization of the levels of the TRYCATs and prevent the causes beyond abnormal levels, instead of inhibition of the TRYCAT pathway.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Author's contributions

All authors contributed to the writing up of the paper. The work was designed by AA and MM. All authors revised and approved the final draft.

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