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Peripheral kynurenines as biomarkers and targets for prevention and treatment of psychiatric conditions associated with SARS-CoV-2 infection

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ABSTRACT

Present review focuses on the possible role of tryptophan (Trp) – kynurenine (Kyn) pathway in the mechanism(s) of COVID-19 associated psychiatric complications. SARS-CoV-2 infection, that causes COVID-19, triggers over-production of interferon-gamma (IFNG), a pro-inflammatory cytokine. IFNG activates *indoleamine 2,3-dioxygenase-1* (*IDO*), enzyme that catalyzes Trp conversion into Kyn, and enzymes of down-stream Kyn pathway that catalyze Kyn conversion into 3-hydroxykynurenine, kynurenic and anthranilic acids in brain and peripheral organs. We reviewed data on SARS-CoV-2 - IFNG – induced changes of peripheral Trp – Kyn pathway, considering their translational potential for personalized psychiatric care. Elevated blood levels of Trp – Kyn pathway metabolites were correlated with the severity of symptoms and predicted the negative outcomes in COVID-19 patients. Association of Trp – Kyn pathway up-regulation with psychiatric complication in non-COVID-19 patients suggests that activation of these pathways contribute to the mechanism(s) of COVID-19 associated psychiatric conditions as well. Increased risk of psychiatric complications in carriers of T (high producer) allele of polymorphic IFNG gene and elevation of serum levels of Kyn and its metabolites in interferon-alpha treated hepatitis C virus patients provides further support for such a suggestion. Assessment of blood levels of Kyn and its metabolites, and polymorphism of Trp – Kyn pathway genes might be developed into personalized biological markers predicting gender/aging dependent individual's risk of psychiatric complications in COVID-19 patients. Up-regulation of IFNG and IDO is necessary for anti-viral protection. Therefore, inhibition of down-stream Kyn pathway should be considered as a new target for prevention/treatment of COVID-19 and COVID-19-associated psychiatric complications.

Introduction

Accumulating evidences pointed out to emergence of severe psychiatric conditions in coronavirus disease 2019 {COVID-19) patients [1]. Proposed mechanism(s) of such complications did not include dysregulation of Trp – Kyn pathway [2]despite the data on SARS-CoV-2 infection-induced overproduction of IFNG [3], an inducer of key enzymes of Trp – Kyn pathway [4], and association of IFNG-inducible up-regulation of Trp – Kyn pathway with psychiatric conditions in non-COVID-19. While IFNG stimulates Trp – Kyn pathway in microglia, specifically affected by SARS-CoV-2 [5] and peripheral organs, current review focuses on SAR – IFNG – induced changes of peripheral (e,g, plasma, serum) changes of Trp – Kyn pathway considering their translational potential for personalized psychiatric care.

Tryptophan – Kynurenine pathway

Tryptophan conversion into kynurenine

Tryptophan (Trp) is an essential (for humans) amino acid. About 3–5% of Trp is metabolized into serotonin (along methoxyindole pathway), while about 95% of non-protein Trp is metabolized along kynurenine (Kyn) pathway resulting in biosynthesis of NAD+, an ubiquitarian coenzyme involved in basic cellular processes [6] (Fig. 1). Formation of Kyn from Trp is catalyzed either by *Trp-2,3-dioxygenase 2* (*TDO*) or by *indoleamine 2,3-dioxygenase* I (IDO) and 2. *IDO*, in difference with liver *TDO*, is present in most mammalian organs, including brain, lungs, blood mononuclear phagocytes, intestine, placenta, adipocytes. [2]. *TDO* is activated by stress hormones (e.g., cortisol) and substrate (Trp) while *IDO* is transcriptionally induced by pro-inflammatory cytokines, e.g., interferon-gamma (IFNG) [2].

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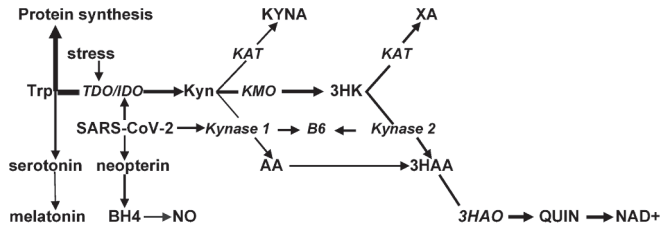

Fig. 1. Kynurenine pathway of tryptophan metabolism. Abbreviations: Trp – tryptophan; Kyn – kynurenine; KYNA – kynurenic acid; 3HK – 3-hydroxykynurenine; XA – xanthurenic acid; AA – anthranilic acid; 3HAA – 3-hydroxyanthranilic acid; QIUN – quinolinic acid; BH4 – tetrahydrobiopterin; NO – nitric oxide; NAD+ – nicotinamide adenine dinucleotide; *TDO/IDO – tryptophan/indoleamine-2,3-dioxygenases; KMO – kynurenine 3-monooxygenase; Kynase – kynureninase; KAT – kynurenine aminotransferases; 3HAO – 3-hydroxyanthranilate 3,4-dioxygenase.*

Kynurenine down-stream pathway

One of the consequences of IFNG – induced *IDO* activation is an increased availability of Kyn as a substrate for production of Kyn down-stream derivatives: 3-hydroxykynurenine (3HK), catalyzed by *kynurenine 3-monooxygenase (KMO)*; kynurenic acid (KYNA), catalyzed by *kynurenine aminotransferases (KAT)*, and anthranilic acid (AA), catalyzed by *kynureninase* 1(*kynase)*. Under physiological conditions *KMO* affinity to Kyn (Km 25 μM) is higher than that of *Kynase* (Km 250 μM) favoring conversion of Kyn into 3HK rather than into AA [7,8].

3HK is further catalyzed by *kynase 2* into 3-hydroxyanthranilic acid, an immediate precursor of neurotoxic quinolinic acid (QUIN), an agonist to NMDA receptors (NMDAR) [9,10].

KAT, in addition to formation of KYNA from Kyn, catalyzes conversion of 3HK into xanthurenic acid (XA), an 8-hydroxylated analog of KYNA, an agonist to mGlu2/3 metabotropic glutamate receptors [11].

SARS-CoV-2 infection and kynurenine metabolism

SARS-CoV-2 infection and kynurenine formation from tryptophan

Considering that SARS-CoV-2 infection triggers production of IFNG, a pro-inflammatory cytokine, that activates IDO, up-regulation of Kyn formation from Trp could be expected in SARS-CoV-2 infection. Notably, prospective study revealed a 1.3-fold increase in serum levels of cortisol ($p = 0.006$) and 1.5-fold increase of Kyn and decreased Trp levels in severe cases and COVID-19 who died [12]. Ratio of plasma (or serum) Kyn to Trp levels is used for clinical assessment of the activity of Trp conversion into Kyn. However, Kyn/Trp ratio does not differentiate between stress- (*TDO*) or inflammation-induced (*IDO*) activation of Trp conversion into Kyn. Notably, IFNG, concurrently with *IDO*, induces *guanosine triphosphate cyclohydrolase 1,* a rate-limiting enzyme of biosynthesis of tetrahydrobiopterin, a cofactor of *nitric oxide synthase* (Fig. 2) [13]. Therefore, evaluation of plasma/serum levels of neopterin, a stable pteridine derivate, helps to differentiate whether stress (*TDO*) or inflammation (*IDO*) is responsible for elevated Kyn/Trp ratio [14]. Concurrent elevation of plasma Kyn/Trp ratio and plasma neopterin strongly suggests *IDO* (rather than *TDO*)-dependent activation of Trp conversion into Kyn [15].

Abbreviations: IFNG – interferon gamma; Kyn – kynurenine; NAD+ – nicotinamide adenine dinucleotide; BH2 – 7,8-dihydroneopterin; NO – nitric oxide; *IDO - indoleamine-2,3-dioxygenase*

Indeed, serum and plasma Trp levels were lower while Kyn and neopterin levels were higher in SARS-CoV-2 –positive than in SARS-CoV-2 –negative subjects [16–18]. Kyn/Trp ratios and neopterin levels correlated with serum IFNG levels and severity of infection, and predicted poor outcome of COVID-19 disease [17,18]. Overactivation of Trp conversion into Kyn was suggested as the top pathway affected in COVID-19 patients [12].

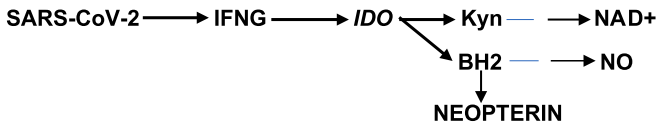

Fig. 2. Neopterin and *IDO* activity.

SARS-CoV-2 infection and Down-stream kynurenine metabolism

Blood levels of KYNA and 3HK were higher in SARS-CoV-2 positive in comparison with SARS-CoV-2 negative subjects [16,17,19], most likely because of increased Kyn levels (due to IFNG-induced *IDO* activation) and *KMO* activation by IFNG [20]. The increase of plasma KYNA levels was over 2-fold in severe cases and in patients who died [12].

Data on AA blood levels in COVID-19 patients are controversial. Comparison of COVID-19 patients with control subjects revealed decreased serum AA levels in COVID-19 patients in difference with the elevated levels of all other studied Kyn [16]. Prospective study, on contrary, found elevated plasma AA levels in patients hospitalized in standard conditions (not at Intensive Care Unit) [19]. Authors suggested that presence of another molecule with the same neutral monoisotopic mass as AA (that, indeed, was decreased in COVID-19 patients) might explain the discrepancy of their results with above cited study. Elevated AA levels correlated with interleukin-18, an IFNG inducing factor. Authors found that elevation of plasma AA (but not other studied Kyn derivatives) was the best negative prognostic marker for unfavorable course of disease (e.g., transfer to ICU, mechanical ventilation, death) in COVID-19 patients. The discovery of elevated AA plasma levels in prospective study of COVID-19 patients [19] is in line with finding of elevated plasma AA levels in prospective study of hepatitis C patients treated with interferon-alpha [21]. Notably, IFNG activates *kynase*, the enzyme that catalyzes AA formation from Kyn [22].

Major psychiatric conditions associated with dysregulations of kynurenine metabolism in non-COVID-19 patients

Review of available data revealed upregulated formation of Kyn, 3HK, KYNA, and, probably, AA in COVID-19 patients. These biochemical changes are known to contribute to mechanism(s) of schizophrenia, depression and anxiety in non-COVID-19 patients.

Schizophrenia. Up-regulated KYNA formation is considered to be causatively linked with major psychopathology in schizophrenia [23]. "KYNA hypothesis" of schizophrenia suggests causative link between major psychopathology of schizophrenia and up-regulated formation of KYNA, an antagonist to NMDA receptors (NMDAR), [24] and a ligand to aryl hydrocarbon and GPR35 receptors [25]. KYNA hypothesis is supported by findings of elevated KYNA concentrations in brains [23] and CSF [26] of schizophrenia patients, and of KYNA-induced schizophrenia-associated disruption of pre-pulse inhibition [27], impairment of cognitive functions [28], damage of spinal cord myelin [29] and impairment of oligodendrocyte viability in animal experiments [30].

AA levels were elevated in plasma and serum of schizophrenia patients [11,31].

Anxiety. Plasma Kyn level and Kyn:Trp ratios were elevated and correlated with severity of anxiety in patients suffered from anxiety, in caffeine-induced anxiety in healthy volunteers and in pregnant women at the end of term, and early puerperium, in comparison with respective controls [32]. Further studies corroborated association of anxiety with dysregulation of Trp – Kyn pathway [33].

Psychiatric conditions associated with Trp – Kyn pathway dysregulations in interferon-treated patients

Depression is the most frequent (up to 50%) psychiatric complication of interferon-alpha treatment of hepatitis C virus (HCV) [34] and melanoma patients [35], although anxiety and psychoses have observed as

well. Positive correlation of Kyn/Trp ratio and neopterin levels with the severity of depression symptoms [36], and decreased content of plasma and blood platelets serotonin [37] suggests that *IDO*-induced shift of Trp from methoxyindole to Kyn pathways contributes to development of depression in interferon treated [38–40].

The recent prospective study found elevation of plasma AA as predictor of increased risk of major depressive disorder in interferon-treated hepatitis C virus patients [21]. AA plasma levels were associated with severity of depression symptoms in female patients with no clinical and biochemical signs of inflammation [41].

In addition to *IDO*-induced depletion of brain serotonin, *IDO*-induced imbalance between neurotoxic and neuroprotective metabolites was suggested to contribute to development of depression, probably via its effects on glutamatergic neurotransmission [9]. Notably, AA may modulate activity of NMDAR by affecting the balance between antagonists, e.g., KYNA, and agonists, e.g., D-serine (D-amino acid), considering that a single dose of one of DAAO inhibitors, benzoate, robustly elevates plasma AA levels in healthy volunteers [42], and that AA (aka, 2-aminobenzoic acid) may be deaminated *in vivo* into benzoate [43].

Trp – Kyn pathway as a target for prevention/treatment of psychiatric conditions associated with SARS-CoV-2 infection

Present review suggests that in addition to factors that were considered as contributing to development of COVID-associated psychiatric conditions [2], over-activation of Trp – Kyn pathway (via IFNG – *IDO* induction) contributes to development of depression, anxiety and psychoses in COVID-19 patients. Therefore, activity of *IDO* that catalyzes formation of Kyn from Trp; and *KMO, KAT* and *kynase* that catalyze Kyn conversion into 3HK, KYNA and AA (respectively) are the most plausible targets for prevention/treatment of psychiatric conditions associated with SARS-CoV- 2 infection. However, inhibition of IFNG and *IDO* are not suitable targets because such intervention might severely impair immunological defense mechanisms against viral infection [44–46]. Inhibition of *KAT* and *Kynase* might be a preferable intervention. Notably, benserazide and carbidopa that already used in treatment of Parkinson's disorder, inhibit *Kynase* and *KAT* in *in vitro* model [47]. We found that sub-chronic administration of benserazide to C57/Bl/j6 mice attenuated olanzapine-induced development of metabolic syndrome [48] apparently associated with up-regulated formation of AA and XA [49]. Future studies might explore the effect of benserazide and other inhibitors of down-stream Kyn metabolism on psychiatric conditions associated with SARS-CoV-2 infection.

Trp – Kyn pathway metabolites as biological markers of psychiatric conditions associated with SARS-CoV-2 infection

Association of Trp – Kyn pathway dysregulation with psychiatric diseases and elevated levels of Kyn, KYNA and AA in COVID-19 patients suggest that assessment of these metabolites might be used to identify COVID- 19 patients at risk for development of psychiatric condition. Notably, Kyn and AA penetrate brain-blood barrier, and, therefore, their blood levels is expected to correlate with their brain levels [50]. On the other hand, it is reasonably to suggest that SARS-CoV-2 infection-induced overactivation of Trp – Kyn pathway is a systemic effect, not limited just to peripheral Kyn metabolism. Therefore, evaluation of plasma/serum levels of Kyn metabolites might be explored as biological markers for prediction of the risk of psychiatric complication in COVID-19 patients. Notably, polymorphism of IFNG (+874) T/A (rs2430561) gene affects the amount of IFNG protein produced in response to viral infection, and might identify patients at risk for psychiatric side effects. We previously reported that carriers of T (high producer) allele were more frequent among depressed than non-depressed IFN-alpha-treated hepatitis C patients [51]. There was no association of not functional IFNG polymorphisms (rs3824259; rs10089084 and rs35099072) with IFN-α-induced depression in hepatitis C virus patient [52]. Considering that IFNG activates *kynase*, that catalyzes formation of AA, a presumed negative predictor of COVID-19 outcome [19], it might be importance to explore the effect of polymorphism of IFNG and other genes impacting production of key enzymes of Trp – Kyn pathway on risk of psychiatric sideeffects in COVID-19 patients. Development of markers usable for personalized psychiatry has to consider several already known factors affecting Trp – Kyn pathway such as gender and aging. Thus, IDO activation (increased Kyn:Trp ratio) was more prominent (and positively correlated with age) in males than females SARS-CoV2- positive patients [18].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Paul Summergrad Consultant: Mental Health Data Services, Inc. Compass Pathways Ltd., Pear Therapeutics, Cowen Stock or Stock Options: Mental Health Data Services, Inc. Quartet Health, Inc., Pear Therapeutics, Karuna Therapeutics, ATAI, Cybin. Gregory Oxenkrug has nothing to declare.

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