



Kynurenic Acid: The Janus-Faced Role of an Immunomodulatory Tryptophan Metabolite and Its Link to Pathological Conditions

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Tryptophan metabolites are known to participate in the regulation of many cells of the immune system and are involved in various immune-mediated diseases and disorders. Kynurenic acid (KYNA) is a product of one branch of the kynurenine pathway of tryptophan metabolism. The influence of KYNA on important neurophysiological and neuropathological processes has been comprehensively documented. In recent years, the link of KYNA to the immune system, inflammation, and cancer has become more apparent. Given this connection, the anti-inflammatory and immunosuppressive functions of KYNA are of particular interest. These characteristics might allow KYNA to act as a “double-edged sword.” The metabolite contributes to both the resolution of inflammation and the establishment of an immunosuppressive environment, which, for instance, allows for tumor immune escape. Our review provides a comprehensive update of the significant biological functions of KYNA and focuses on its immunomodulatory properties by signaling via G-protein-coupled receptor 35 (GPR35)- and aryl hydrocarbon receptor-mediated pathways. Furthermore, we discuss the role of KYNA–GPR35 interaction and microbiota associated KYNA metabolism for gut homeostasis.

Keywords: kynurenic acid, immunomodulation, inflammation, aryl hydrocarbon receptor, G-protein-coupled receptor 35, tryptophan metabolism, microbiota

BIOLOGICAL SIGNIFICANCE OF THE KYNURENINE PATHWAY (KP)

The degradation of tryptophan (TRP) along the KP plays a crucial role in the regulation of the immune response, notably as a counter-regulatory mechanism in the context of inflammation (1–3). An overview of the KP is presented in **Figure 1**. Three rate-limiting enzymes of KP, tryptophan 2,3-dioxygenase (TDO) and indolamine 2,3-dioxygenase (IDO) 1 and 2, have been described in the literature thus far. TDO is positively regulated by TRP in order to maintain the homeostasis of TRP (4, 5). Furthermore, the expression and activity of TDO is regulated by hormones such as cortisol, insulin, glucagon, or epinephrine (6–8). IDO1 and 2 are upregulated by inflammatory stimuli such as interferon- γ (IFN- γ) (9–14). The significance of KP activation depends on the production of biologically active metabolites such as kynurenine (KYN), kynurenic acid (KYNA), quinolinic acid (QUIN), or anthranilic acid mediating various immuno- and neuromodulative functions. Within the central nervous system, it has been well documented that metabolites such as KYNA and QUIN modulate neurological functions. Thus, KYNA acts as an antagonist affecting all ionotropic glutamate receptors including NMDA, AMPA, and kainate receptors as well as the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) assuming it as a neuroprotective metabolite (15–18). However, the inhibition of $\alpha 7$ nAChR by KYNA is extensively debated because some later studies addressing

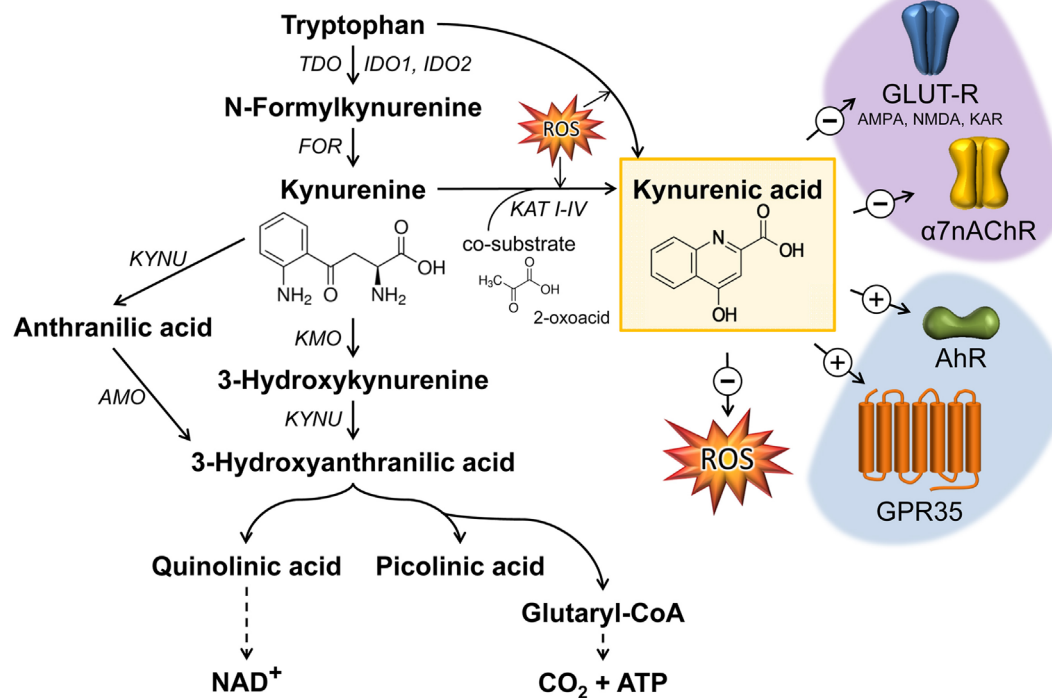


FIGURE 1 | Kynurenic acid (KYNA) synthesis along the kynurenine pathway and its mode of action. The catabolism of TRP by the enzymes TDO or IDO represents the rate-limiting step in KYNA synthesis. The intermediate metabolite kynurenine can be further processed through three distinct pathways to form KYNA, 3-hydroxykynurenine, and anthranilic acid. KYNA is formed by the irreversible transamination of KYN either via kynurenine aminotransferases (KAT I–IV) or through the action of reactive oxygen species (ROS). KYNA is a non-competitive antagonist of ionotropic glutamate receptors (GLUT-R) as well as of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) expressed on neuronal cells. Apart from neuromodulatory properties, KYNA is an agonist of the broadly expressed G-protein-coupled receptor 35 (GPR35) and aryl hydrocarbon receptor (AhR). Furthermore, KYNA functions as an ROS scavenger. Black arrows mark enzymatic reactions and dashed arrows include more than one catalytic reaction step. FOR, formamidase; IDO, indolamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; KYN, kynureninase; AMO, anthranilate 3-monooxygenase; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDA, *N*-methyl-D-aspartate receptor; KAR, kainate receptor.

this mechanism (3, 19–21) could not recapitulate the original results from Hilmas et al. (18). Dysregulation of KP, resulting in alterations of the balance between KYNA and QUIN, has been described in many neurological disorders (22). However, alterations of KYNA are also described in several inflammatory-related states, such as sepsis or inflammatory bowel disease (IBD), and are discussed as a potential marker in cancer patients (23–25). It is generally accepted that KYNA mediates immunosuppressive effects (22), notably by targeting the G-protein-coupled receptor 35 (GPR35)- or aryl hydrocarbon receptor (AhR)-associated signaling pathways (2, 26, 27).

ENDOGENOUS KYNA SYNTHESIS AND ITS INFLAMMATORY REGULATION IN VERTEBRATES

Generation of KYNA was described in endothelial cells (28), epithelial cells (29, 30), fibroblasts (31), pancreatic islet cells (32), human peripheral blood mononuclear cells (33), skeletal muscle cells (34), and red blood cells (35). Under physiological conditions, KYNA is produced by kynurenine aminotransferases

(KATs), which catalyze the irreversible transamination reaction between L-KYN and 2-oxoacid, as a co-substrate, to form KYNA (36, 37), or in the presence of reactive oxygen species (ROS) as illustrated in **Figure 1**. Currently four proteins named KAT I–IV are described in mammals (38–43). Mediating overlapping biological functions, the mammalian enzymes KAT I and KAT III share high homologies in sequence and genomic structure (42). KAT activity was described in various tissues, such as liver, kidney, small intestine, dermal fibroblasts, and brain (31, 38, 44, 45). In human cardiac muscle, there is evidence that the KAT system differs from brain KAT regulation regarding optimum pH, co-substrate specificity, and sensitivity to inhibition by amino acids such as L-TRP (36). Regarding the inflammatory regulation of KATs, there is no consensus, assuming the existence of cell type-dependent regulatory differences. Studies in human dermal fibroblasts reveal that tumor necrosis factor α (TNF) alone does not affect the number of transcripts, whereas IFN- γ alone (or in combination with TNF) decreases the transcript abundance of KAT I, III, and IV after 48 h. Due to the fact that in this study the metabolite concentration of KYNA was increased in supernatants the decrease of KATs 48 h after cytokine stimulation may reflect a negative feedback mechanism (31). In fetal astrocytes, IFN- γ

increases the transcript levels of KAT I and II after 24 h (46), whereas no effect of IFN- γ was observed in neuronal cells (47). In mice, an intraperitoneal (i.p.) lipopolysaccharide (LPS) challenge increased KAT-I mRNA expression in the hippocampus 6 h postchallenge, followed by a decrease after 24 h, whereas KAT-II mRNA expression was decreased 24 h after LPS treatment (48).

In addition to KAT-catalyzed KYNA synthesis, alternative routes for KYNA synthesis in the presence of ROS have been described (49) (**Figure 1**). Thus, it is assumed that indole-3-pyruvic acid, a reaction product of tryptophan-2-oxoglutarate-induced transamination of TRP, undergoes pyrrole ring cleavage followed by a spontaneous cyclization generating KYNA (50). Furthermore, L-KYN can be converted to KYNA in the presence of hydrogen peroxide (51) or KYNA formation can result from reactions of KYN or indole-3-pyruvic acid under conditions generating free radicals (52, 53).

Elevations of KYNA blood concentrations were experimentally induced under different inflammatory conditions. In pigs, the i.p. application of LPS increased plasma levels of KYNA. However, the *ex vivo* LPS stimulation of whole blood culture failed to elevate KYNA in supernatants (54), assuming sources of KYNA production other than blood cells or the requirement of additional inflammatory mediators, which are not produced in blood cells. Increased KYNA plasma concentrations were also detected in mice that were repeatedly stressed. In this context, the elevated KYNA levels were proposed to be induced by a systemic low-grade inflammation due to an altered intestinal barrier function (55). Interestingly, in this study the application of the IDO inhibitor L-1-methyltryptophan (1-MT), a TRP analog, specifically increased plasma concentrations of KYNA by a yet unknown pathway (55).

KYNA DEGRADATION AND EXCRETION

Kynurenic acid is described as one of the end products of KP in animals, assuming no uptake or further metabolism of KYNA. In a study including different rodent species, 90% of radioactively labeled KYNA was excreted in urine within 24 h of i.p. application (56). Thus, 80–100% of labeled KYNA was excreted unchanged and only small amounts of quinaldic acid and quinaldyglycine were detected (0.3 and 5%, respectively). This is supported by studies in rats, finding that radioactively labeled KYNA was eliminated rapidly after intracerebroventricular microinjection and substantial amounts of radioactivity were recovered in urine 30 min after injection (57). Studies in rabbits described differences in KYNA metabolism depending on the type of administration (58). After oral administration of KYNA, the majority of the dose was detected in the form of quinaldic or 8-hydroxyquinaldic acid, indicating a dehydroxylation of the molecule. In contrast, after subcutaneous administration, 99% of KYNA was recovered unchanged, indicating that the dehydroxylation occurs in the gastrointestinal tract (58) most probably by the gut microbiota. This is supported by the finding that approximately 30% of ingested KYNA was excreted in urine as quinaldic acid in humans (59). The assumption that KYNA is metabolized by microorganisms is supported by the finding that extracts of *Pseudomonas* spp. and *Aerococcus* spp. were able to enzymatically partially degrade KYNA (60, 61).

IMMUNOMODULATIVE PROPERTIES OF KYNA

In recent years, numerous *in vivo* and *in vitro* studies have been directed toward the immunomodulatory functions of KYNA. There are strong indications that the action of KYNA varies depending on whether inflammatory or homeostatic conditions are considered. Under homeostatic conditions, KYNA induced interleukin 6 (IL6) mRNA expression 2 h after treatment in the breast cancer cell line MCF-7 (27) and cytokine secretion (TNF, IL6, IL1 β , and IL10) in primary murine splenocytes after 72 h (62). A further *in vitro* study indicated that KYNA may be an early mediator of leukocyte recruitment, acting by triggering the activation of neutrophils as well as the adhesion of monocytes to fibronectin and intercellular adhesion molecule 1 *via* β 1-/ β 2 integrin (63). In contrast, KYNA treatment decreased the mRNA expression of IL6 after 6 h in the rat mast cell line RBL-2H3 followed by a return to baseline level after 24 h (64). In addition, 24-h KYNA treatment under homeostatic conditions did not influence IL6 or TNF secretion in the murine microglial cell line BV-2 (65). At first glance, all these findings seem to be very inhomogeneous. However, they clearly demonstrate that knowing that mRNA expression of pro-inflammatory cytokines is normally tightly controlled by mRNA decay and cytokine secretion measurement needs sufficient accumulation time, it is very important for interpretation of such results to know at which time what (mRNA expression or cytokine secretion) was analyzed. In conclusion, these studies, analyzing the effect of KYNA under non-inflammatory conditions, suggest a time- and/or cell type-dependent influence of the treatment.

The KYNA effect under inflammatory conditions appears to be more uniformly. Several *in vitro* studies, using various primary or immortalized leukocyte cell types, have revealed that KYNA can attenuate inflammation elucidated by different stimuli (e.g., LPS). For instance, KYNA reduces TNF expression and secretion (26, 55, 65, 66) and diminishes high-mobility group box 1 (HMGB1) protein secretion in monocytes (66, 67). Likewise, KYNA has been shown to inhibit the secretion of α -defensin HNP1–3 in granulocyte cultures (66) and reduce interleukin 4 release in T-cell receptor stimulated invariant natural killer-like T cells (iNKT) (68). Recently, Elizei et al. (69) demonstrated that KYNA reduced LPS-induced IL23 expression of dendritic cells and inhibited Th17 cell differentiation *in vitro*. The downregulation of the IL23/IL17 axis is known to be beneficial for anti-inflammatory treatment of many immune-mediated diseases (70).

These anti-inflammatory effects of KYNA, frequently observed in many cell models, were confirmed by *in vivo* studies in mice and dogs. For example, KYNA treatment inhibited the LPS induced increase of TNF and nitric oxide (NO) in mice serum and also drastically reduced LPS-induced death in those animals (67). Leukocytes of KYNA-treated mice also exhibited a reduced release of TNF in response to an *ex vivo* LPS challenge (55). Moreover, the increased mucosal leukocyte accumulation and the xanthine oxidoreductase activity, a predominant marker of mucosal superoxide radical production, in the gastrointestinal tract of dogs with experimental colon obstruction were reduced by KYNA treatment (71).

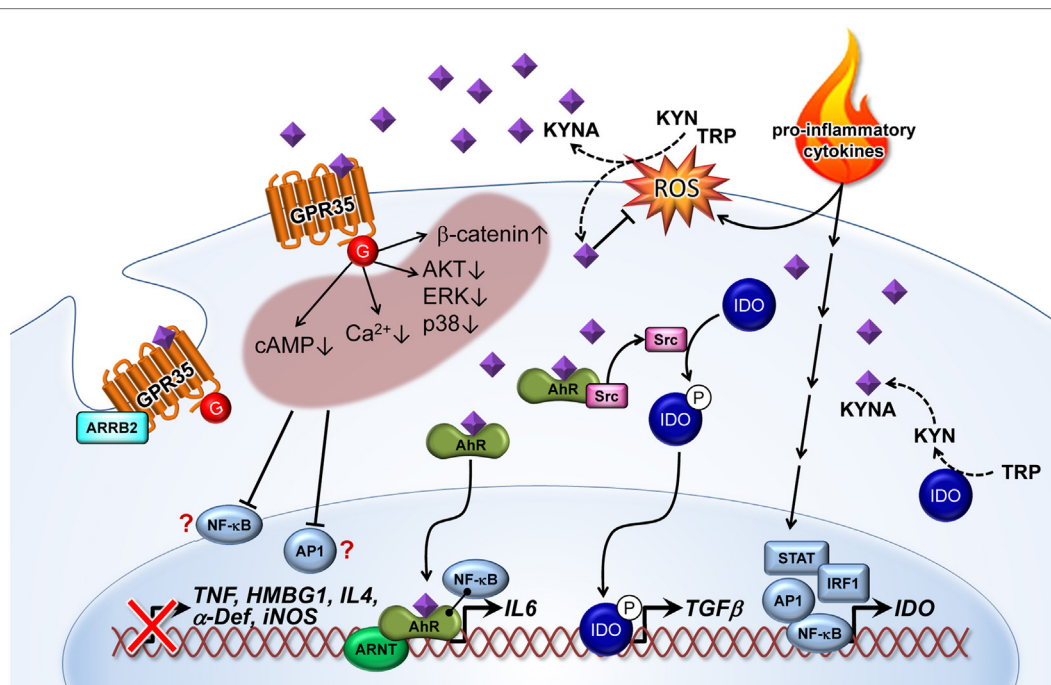


FIGURE 2 | Kynurenic acid (KYNA)-mediated pathways of inflammatory signaling. Pro-inflammatory cytokines induce the expression of indolamine (IDO) enzyme via STAT, AP1, IRF1, and NF- κ B transcription factor activation. KYNA is formed by the IDO-dependent canonical pathway or by an alternative route through direct kynurenine (KYN) or tryptophan (TRP) transformation by reactive oxygen species (ROS). On the other hand, KYNA as a free radical scavenger decreases ROS level. KYNA binds and activates G-protein-coupled receptor 35 (GPR35)-reducing cAMP and calcium (Ca^{2+}) levels in cells. Activation of GPR35 by KYNA may also inhibit phosphorylation of protein kinase B (AKT), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated protein kinase (p38), as well as increasing the level of β -catenin. All of these cellular responses probably decrease activation of relevant inflammatory transcription factors, such as NF- κ B and AP1. Therefore, reduced induction of tumor necrosis factor α (TNF), high-mobility group box 1 (HMBG1), interleukin 4 (IL4), α defensin (α -Def), and inducible nitric oxide synthase (iNOS) have frequently been observed in response to KYNA treatment. Recruitment of arrestin β 2 (ARRB2) to GPR35 is necessary for internalization and desensitization of the KYNA-activated receptor. Binding of KYNA to the aryl hydrocarbon receptor (AhR) receptor leads to recruitment of the AHR nuclear translocator (ARNT) and induction of IL6 expression. Interaction of the KYNA-AhR complex with NF- κ B may also be involved in the induction of IL6. Furthermore, ligand-activated AhR initiates the proto-oncogene tyrosine-protein kinase Src activation and, thereby, the phosphorylation (P) of IDO. Phosphorylated IDO induces the expression of transforming growth factor β 1 (TGF β). NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; AP1, activator protein 1; STAT, signal transducer and activator of transcription; IRF, interferon-regulatory factor; G, G protein.

Kynurenic acid is a ligand of the GPR35 (26) and the AhR (27, 72) (Figures 1 and 2). The affinity of KYNA for both receptors is in the low micromolar range. However, in various inflammatory and tumor diseases high levels of this metabolite are produced, so it is not surprising that under these conditions KYNA levels are sufficient to activate these receptors (72). In addition to GPR35- and AhR-mediated signals, KYNA has a relevant role as an antioxidant and ROS scavenger (73, 74) (Figures 1 and 2). This indicates that KYNA also actively prevents tissue damage triggered by overshooting inflammation. In addition, induction of the KYNA-synthesizing branch of TRP metabolism may also be relevant for the synthesis of other TRP metabolites, such as serotonin or melatonin. Serotonin and melatonin are known immune regulators whose decrease may influence immune response (75, 76). KYNA synthesis may decrease their abundance either simply by the reduction of the necessary substrate TRP, or by direct inhibition of their synthesis, or induction of their degradation. In this regard, it was found that furafylline-mediated inhibition of CYP1A2, a “classic” AhR-inducible gene, increased 6-hydroxymethylation of melatonin in rat liver slides. This result indicates that AhR

signaling, perhaps triggered by KYNA, may be relevant in melatonin catabolism (77).

KYNA AS AGONIST OF GPR35

G-protein-coupled receptor 35 is expressed in various subpopulations of immune cells, including peripheral monocytes (26), mast cells, basophils, eosinophils (78), and iNKT cells (68). A high level of GPR35 expression was detected throughout the digestive tract (26, 79), as well as in lung, skeletal muscle, uterus, and dorsal root ganglion (79). Moderate expression was found in heart, liver, bladder, spinal cord, whole brain, and cerebrum (79).

Recently, it was found that GPR35 is a high-affinity receptor for the mucosal chemokine CXCL17 (80). Nevertheless, KYNA was the first reported agonist ligand for GPR35. This was identified by high-throughput screening using changes of intracellular calcium (Ca^{2+}) in the Chinese hamster ovary cell line, CHO, co-expressing GPR35 and a G-protein mixture as a readout (15). Further in-depth studies revealed that KYNA-GPR35 interaction inhibited N-type Ca^{2+} channels in sympathetic neurons (81) and reduced the plateau phase of ATP-induced calcium transients in

astrocytes (82). The later study also demonstrated that KYNA-mediated GPR35 activation decreased forskolin-induced cAMP elevation. Furthermore, the recruitment of β -arrestin 2 mediated GPR35 internalization upon KYNA activation, which led to receptor desensitization (82, 83).

Kynurenic acid may also have an inhibitory effect on the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways. Walczak et al. (84) demonstrated that KYNA decreased phosphorylation of extracellular signal-regulated kinases (ERK) 1/2, p38 MAPK, and Akt in colon epithelial cells. They also found indications that KYNA induced accumulation of β -catenin. MAPK, PI3K/Akt and β -catenin pathways are well-known targets of GPR signaling (85, 86). Therefore, it is possible that the observed inhibition of ERK and p38, as well as the induction of β -catenin accumulation after KYNA treatment, are a consequence of GPR35 activation. Interestingly, all of these described effects of KYNA-GPR35 signaling might lead to the suppression or limitation of inflammation. Increased intracellular calcium is associated with inflammatory signal secretion (87, 88) and triggers the activation of NF- κ B (89), which is an essential transcription factor in inflammation (90). The cAMP pathway is known to regulate innate and adaptive immune cell activities (91) [e.g., T-cell functions (92)]. In this respect, there is strong evidence that KYNA-GPR35-mediated inhibition of adenylyl cyclase is causal for the downregulation of the IL23/IL17 immune axis observed after KYNA treatment (69). Furthermore, the PI3K/Akt pathway and MAPK's play crucial roles in generating an inflammatory response (93, 94). Conversely, the β -catenin signaling pathway is known to inhibit inflammation through limiting NF- κ B activation by stabilizing the NF- κ B inhibitory κ B-factors (95).

KYNA AS AGONIST OF AhR

Aryl hydrocarbon receptor is a ubiquitously expressed promiscuous ligand-operated receptor of KYNA (27), mediating crucial effects on the regulation of the immune response (96). When binding to a ligand, AhR dimerizes with the AhR nuclear translocator (ARNT) and acts as a transcription factor.

Several studies using AhR knockout mice indicated that this receptor has an important immune regulatory role in inflammation. For instance, AhR-deficient mice have a high susceptibility to LPS-induced septic shock (97) and developed a stronger response after local inflammatory challenge (or insult) in the lung (98, 99). AhR activation is involved in preventing an overshooting pro-inflammatory cytokine induction in response to an inflammatory stimulus in various cells including fibroblasts, endothelial cells, and macrophages (97, 100, 101). Therefore, it has been proposed that a clinical treatment with an appropriated AhR ligand like KYNA may offer a promising therapeutic intervention in inflammatory disorders. Interestingly, brains of AhR knockout mice exhibited an increased KAT-II expression and a higher KYNA level in the cerebral cortex and striatum that is associated with protection against oxidative stress induced by an excitotoxic insult *via* intrastriatal application of QUIN (102). This may be either a result of KYNA-mediated counteraction of NMDAR activation by QUIN, which is known to mediate excitotoxic properties, or

of the receptor-independent antioxidative properties of KYNA discussed above. Furthermore, the data of this study indicated a negative feedback-loop between AhR, KAT II, and the AhR ligand KYNA in the brain. Unfortunately, there are no data regarding KYNA levels and KAT expression outside the brain of AhR-deficient mice. Therefore, further analyses are necessary to prove whether this is only a tissue-specific observation or a general finding. However, studies using AhR-deficient mice need to be carefully evaluated because, although these animals appeared relatively normal, this knockout influences several physiologic processes in the animals including structure of the central nervous system and blood cell differentiation (103).

In addition to KYNA, other TRP metabolites, such as the KYNA precursor KYN, have been shown to be ligands of the AhR (104). In humans, pigs, and mice KYNA normally have 3- to 10-fold lower plasma concentrations than KYN (54, 55, 105, 106). However, KYNA is described as a more potent AhR ligand (27) and has a higher stability than KYN (56). It was speculated that AhR interaction with TRP metabolites contributed to immune homeostasis during endotoxin tolerance by activating immunomodulatory signaling (104). The data of Bessedé et al. indicated that AhR-associated Src activity, triggered by TRP metabolites bound to AhR, was responsible for IDO1 phosphorylation. These studies revealed that the TRP metabolite KYN, without the IDO1 protein, was insufficient to induce TGF β expression. The authors speculated that IDO1 phosphorylation represented an independent signaling pathway necessary for TGF β -mediated immune tolerance. Whether the TRP metabolite KYN or KYNA could be the relevant AhR ligand mediating those immunosuppressive effects remains unclear. It has been demonstrated that KYNA ligated to AhR induced IL6 mRNA expression in breast cancer cells. These authors also showed that a combination of KYNA and pro-inflammatory IL1 induced IL6 much more strongly than either of these factors alone. This synergistic activation of IL6 could be mediated by direct interaction of AhR-ARNT and the NF- κ B factor RELB. NF- κ B factors are known to be activated by pro-inflammatory cytokines, such as IL1. The role of AhR-NF- κ B cross talk was previously described for IL8 gene expression (107). IL6 features pleiotropic activities (108). Although IL6 plays essential roles in promoting inflammation, it also has many anti-inflammatory and regenerative activities (109) reviewed in Ref. (110, 111). Therefore, it is difficult to estimate if KYNA-mediated IL6 expression contributes only to the immunosuppressive function of KYNA. However, studies have shown that IL6 is involved in the development of many chronic inflammatory and cancer diseases (111). For example, the study that demonstrated a KYNA-mediated induction of IL6 in breast cancer cells discussed this observation as part of the mechanisms allowing tumor cells to escape immune surveillance (27). A further interesting point is that IL6 can induce IDO1 *via* STAT3 activation. This signaling is known as the AhR-IL6-STAT3 loop, which is associated with poor prognosis in lung cancer (112). There is increasing evidence that the interaction of AhR with metabolites of the KP, such as KYNA, is relevant for maintaining the immunosuppressive microenvironment in many cancer types (72, 113). The probable mode of action is a TGF β - and IL6-mediated suppression of T-cell response by interfering with differentiation and activation

TABLE 1 | Alteration of kynurenic acid (KYNA) metabolism in several pathological states in humans.

Disease	Perturbation of KYNA level	Matrix	Source
Inflammation-related diseases			
Multiple sclerosis	Increased vs. healthy controls	Plasma	(114)
Inflammatory bowel disease	Increased vs. healthy controls	Plasma	(23)
Septic shock patients with acute kidney injury	Increased in non-survivor vs. survivors	Plasma	(24)
Out-of-hospital cardiac arrest	Increased in patients with 12-month poor outcome	Plasma	(115)
Rheumatoid arthritis	Decreased vs. patients with osteoarthritis	Synovial fluid	(116, 117)
	Positive correlation with plasma fibrinogen		
	Positive correlation with morning stiffness and pain score	Serum	
Type 2 diabetes	Increased vs. healthy control	Plasma	(118)
Chronic kidney disease	Increased with severity stage	Serum	(119)
Odontogenic abscesses	Increased vs. healthy subjects	Saliva	(120)
Cancer			
Colon carcinoma	Increased vs. non-carcinoma cells	Supernatant	(30)
Adenoma tubovillosum and A. tubulare	Increased vs. non-carcinoma cells	Supernatant	(30)
Non-small cell lung cancer	Increased vs. healthy controls	Serum	(121)
	Increased in patients with metastatic spread to lymph nodes vs. non-metastatic patients		
Prostate cancer	Decreased vs. participants without malignancy	Urine	(25)
Primary cervical cancer	Decreased vs. healthy controls	Serum	(122)
Glioma	Decreased vs. healthy controls	Serum	(123)
Mental disorders			
Affective psychosis	Decreased vs. healthy controls	Serum	(124)
Chronic schizophrenia	Decreased vs. healthy control	Serum	(125)
Chronic migraine	Decreased vs. healthy controls	Serum	(126)
Cluster headache	Decreased vs. healthy controls	Serum	(127)
Alzheimer's type dementia	Positive correlation of KYNA with cognitive function	Plasma	(128)
Schizophrenia with distress intolerance	Increased vs. patients with distress tolerance and healthy controls, positive correlation with severity of clinical symptoms	Saliva	(129)
Schizophrenia	Increased vs. healthy controls	CSF	(130–132)
Alzheimer's dementia	Decreased vs. healthy control	Plasma, red blood cells	(35)
Alzheimer's disease	Positive correlation with P-tau and soluble intercellular adhesion molecule-1	CSF	(37)
Inherited diseases/diseases with questionable cause			
Down syndrome	Increased vs. control specimens	Temporal cortex, urine	(133, 134)
Huntington's disease	Reduced vs. healthy controls	Brain areas, CSF	(135, 136)
Amyotrophic lateral sclerosis (ALS)	Increased patients with bulbar onset and severe clinical status of ALS vs. healthy control	CSF	(137)
	Decreased in patients with severe clinical status of ALS vs. healthy control	Serum	
Irritable bowel syndrome	Decreased vs. healthy controls	Plasma, serum	(138, 139)

of regulatory T cells. This is still supported by the fact that various cancer cells secrete KYNA (Table 1).

Irrespective of the presumed KYNA-mediated tumor-immune escape, another research group found that high KYNA concentrations inhibit proliferation and migration of cancer cell lines *in vitro* (84, 140, 141). This seems to be mediated by interference with the cyclin-dependent kinase inhibitor p21(WAF1/CIP1) pathway (142). All this indicates that KYNA can act as both tumor-promoting as well as tumor-inhibiting factor. However, all mentioned studies used cancer cell lines and characterized the effect of KYNA under *in vitro* conditions. Therefore, it must be kept in mind that further studies are needed to validate the KYNA effects on tumor development.

KYNA AND ITS LINK TO PATHOLOGICAL CONDITIONS

Alterations of KYNA metabolism in both periphery and brain are described for several pathological states in humans (Table 1).

Inflammation-Related Diseases

Kynurenic acid levels are increased in peripheral blood of patients suffering from type 2 diabetes, multiple sclerosis, IBD, and chronic kidney disease (23, 114, 118, 119) as well as in saliva of patients suffering from odontogenic abscesses (140). Regarding these chronic inflammatory conditions, it remains unclear whether the elevation of KYNA is either a compensatory response due to inflammatory signaling or a primary abnormality, inducing specific patterns of diseases. However, it is presumed that chronic stress or low-grade inflammation may induce the production of KYNA (55, 118), provoking various immunomodulative actions due to KYNA-mediated signaling pathways. Contrary to elevated peripheral KYNA levels in IBD, blood levels of KYNA were found to be decreased in patients with irritable bowel syndrome (IBS), which is—in contrast to IBD—a functional gastrointestinal disorder without chronic inflammation (138, 139). However, KYN was increased in plasma of patients with IBS (138) and with severe IBS (143). These data may indicate an inflammatory induction of IDO. However, in this study there was no evidence for

inflammatory processes, such as increased serum levels of IFN- γ or TRP depletion compared with healthy controls. Christmas et al. (139) reported decreased levels of KYNA, KYN, and 3-hydroxyanthranilic acid in IBS. This provides evidence for a generally inhibited TRP degradation, resulting in a reduced TRP oxidation. It was assumed that the increased free TRP would be a source for utilizing serotonin, which may increase gut secretions and motility as described in diarrhea-predominant IBS.

Studies of patients with septic shock and acute kidney injury showed that a failed reduction of KYNA after a hemofiltration treatment might predict fatal outcomes (24). The authors assumed that the increased plasma levels of KYNA depended on the rate of KYNA synthesis and not on a failed renal excretion since KYNA and other TRP metabolites were eliminated continuously in these patients by hemodialysis. An increased KP activation, for instance, measured by increased KYN and KYNA levels, was observed in non-survivors of out-of-hospital cardiac arrest during early and late stage of disease (115). In this context, it is possible that increased generation of KP metabolites may reflect an overshooting pro-inflammatory response, which subsequently provokes the establishment of a protracted immunoparalysis as described in sepsis (2).

A positive correlation of serum KYNA with morning stiffness and pain score was found in patients with rheumatoid arthritis (RA) (116), indicating that an increased level of inflammation is correlated with increased circulating KYNA levels. This assumption is supported by the finding that KYNA concentrations in the synovial fluid of RA patients were positively correlated with plasma fibrinogen (116), which is described as a marker for disease activity reflecting the acute phase response (144). *In vitro* studies revealed that KYNA inhibited the proliferation of synoviocytes and enhanced the antiproliferative action of drugs, targeting the prevention of hyperplasia of synovial fibroblasts (145). In patients with RA, KYNA was decreased compared with patients with osteoarthritis (OA; no inflammatory background). This was in accordance with the results of an earlier study revealing that KYNA was decreased in RA compared with OA, while IDO activity was increased, which is not surprising due to RA-induced inflammation (117). According to the described antiproliferative function of KYNA on synovial fibroblasts, impaired KYNA synthesis may provoke the development of hyperplasia in RA.

Cancer

Increased concentrations of KYNA were detected in supernatants of colon-derived cells from patients diagnosed with colon carcinoma, adenoma tubulovillosum, or adenoma tubulare compared with a healthy control group (30). Furthermore, KYNA was elevated in the serum of patients with non-small cell lung cancer compared with healthy volunteers and increased in patients with metastases that spread to lymph nodes vs. non-metastatic patients (121). These findings support the suggestion that many cancer types secrete KYNA provoking the establishment of an immunosuppressive microenvironment (72, 113). In contrast, KYNA was decreased in the serum of patients suffering from glioblastoma compared with healthy controls (123). Due to the increased ratio of KYN to TRP, an indicator for IDO activity,

an over-activation of KP was postulated. However, the plasma concentrations of TRP, KYN, KYNA, and QUIN were decreased compared with healthy controls, indicating a depletion of TRP by other mechanisms. Indeed, Opitz et al. detected an accumulation of KYN and QUIN in TDO-expressing glioblastoma cells (146), in addition to lower serum levels of TRP and KYN in glioblastoma patients. This indicates an increased transport of TRP and KYN through the blood–brain barrier. In this context it was shown that the TDO-derived KYN interfered with AhR signaling, leading to a suppression of antitumor immune responses and likewise promoted tumor-cell survival (146). Unfortunately, KYNA concentrations were not evaluated in this study. The studies of Adams et al. found no evidence for an increased production of neither the metabolites KYN, QUIN, nor KYNA in the supernatant of glioblastoma cells. However, the mRNA expression of KAT I, II, and III but not the secretion of KYNA was reduced in glioma cells compared with fetal or adult astrocytes (123), suggesting that in glioma cancer cells there is no shift to the KYNA branch compared with other cancer cells. The absence of increased KYNA production in glioma cells might be a benefit for tumor survival, since it has been shown that KYNA inhibits the proliferation and migration of human glioblastoma T98G cells (141). A shift of KYNA to QUIN production was also shown in patients with primary cervical cancer, resulting in reduced levels of serum KYNA whereas QUIN was increased concurrent with unchanged levels of TRP and KYN (122). It was assumed that the increased levels of QUIN may contribute to the restoration of energy supplies *via* formation of acetyl-CoA and NAD pathways. Decreased levels of KYNA were also detected in the urine of prostate cancer patients (25). However, whether the decrease resulted from attenuated KYNA synthesis or an impaired renal clearance was not evaluated in this study.

Mental Disorders

It is well described that there is a link between an inflammation-induced impairment of the balance of TRP metabolism and the development of mental disorders such as depression or schizophrenia (130, 147). KYNA was found to be decreased in the blood of patients with affective psychosis (124), chronic schizophrenia (125), Alzheimer's dementia (35, 128), cluster headache (127), and chronic migraine (126) compared with healthy subjects. Similar to the findings in glioma patients, the decrease of KYNA in blood may indicate an increased transfer of TRP or KYN through the blood–brain barrier as a substrate for local synthesis of KYNA in brain tissue. This is supported by the findings that increased levels of KYNA were detected in the CSF of patients with schizophrenia (130–132). In the CSF of patients with Alzheimer's disease (AD), KYNA correlated with the expression of P-tau and the soluble intercellular adhesion molecule-1, which are biomarkers for inflammation (37). A link between inflammation and increased brain levels of KYNA was furthermore described in amyotrophic lateral sclerosis (ALS) patients. This study demonstrated a correlation between increased levels of KYNA in CSF with the severe clinical status of ALS (137). It is assumed that oxidative stress, glutamatergic excitotoxicity, or neuroinflammation play key roles in the pathophysiology of neurodegeneration, particularly in ALS or

AD (148). Therefore, the increased production of KYNA may act as compensatory response to neurotoxic effects. The fact that KYNA was decreased in the blood of patients with a severe clinical state of ALS (137) supports the suggestion that TRP or KYN from the periphery is used as precursors for increased brain synthesis of KYNA, knowing that KYNA is hardly able to cross the blood–brain barrier (149). Increased levels of KYNA in saliva were also detected in schizophrenia patients with concurrent distress intolerance compared with distress-tolerant patients and healthy controls. This finding indicated an interference of stress with the activation of KP (129).

Inherited Diseases/Diseases with Questionable Cause

In patients suffering from Huntington's disease, KYNA was decreased in the CSF and several brain regions (135, 136, 150). It was suggested that this was due to a selective impairment in KYNA biosynthesis in specific brain areas of HD patients (150), resulting in an inadequate anti-inflammatory and neuroprotective response to inflammatory conditions.

Increased concentrations of KYNA in the brain were described in patients with Down syndrome (133), which exhibit similar neuropathological features as patients with AD, such as neuritic amyloid- β plaques (151). This indicates that neuro-inflammatory processes may play a role in the Down syndrome phenotype. Increased brain levels of KYNA may reflect a compensatory response to neurotoxic effects due to congenital malfunctions. Furthermore, the finding that in Down syndrome patients the urinary excretion of KYN was lower concurrent with increased excretion of KYNA, and anthranilic acid, suggests a shift of KP to the neuroprotective and antioxidative branch (134).

In conclusion, the results of the described clinical studies might indicate that the production of KYNA is a compensatory mechanism that functions to limit inflammation-induced cell and tissue damage in both brain and periphery. Furthermore, an impaired synthesis of KYNA may provoke an inadequate anti-inflammatory response characterized by, e.g., enhanced tissue damage or exceeding cell proliferation during inflammatory conditions. In tumor cells, the modulation of KYNA secretion was found to be different between the types of carcinoma. An enhanced production of KYNA by cancer cells may provoke the establishment of an immunosuppressive microenvironment for effective immune escape. Decreased levels of KYNA in the periphery of patient suffering from cerebral cancer (and also from mental disorders) might reflect an increased transfer of TRP and KYN through the blood–brain barrier. This might be a consequence of an accelerated TRP degradation due to pathological processes in brain tissue. However, also a shift to another branch of KP such as QUIN may result in the reduction of KYNA.

KYNA, MICROBIOTA, AND GUT HOMEOSTASIS

High GPR35 expression in the gastrointestinal tract (26, 79) indicates that this receptor, and probably its ligand KYNA, could have a function in gut homeostasis (152). The potential significance of

KYNA for gut health emerges from its association with various bowel diseases and colon cancer [Table 1 (30, 138, 139)], as well as the potential anti-inflammatory effects of KYNA treatment in dogs with experimental colon obstruction (71). Studies in rats and pigs have shown a high concentration of KYNA in the intestinal lumen (153, 154). The intestinal KYNA concentration increased from the proximal to the distal part of the gut, reaching $\sim 16 \mu\text{M}$ in the distal ileum of the rat (153) and $\sim 1.6 \mu\text{M}$ in the colon of the pig (154). The studies in rat suggest that relevant amounts of KYNA in the gut originated from the intestinal microflora, due to the relatively low concentrations in the wall of the ileum ($\sim 0.2\text{--}0.3 \mu\text{M}$) and the food ($\sim 0.6 \mu\text{M}$). However, certain foods and herbs may contain relatively high amounts of KYNA like broccoli ($\sim 2 \mu\text{M}$), honey ($\sim 1 \mu\text{M}$), basil ($\sim 74 \mu\text{M}$), and thyme ($\sim 9 \mu\text{M}$) (155, 156). Furthermore, the intestinal commensal *Escherichia coli* can produce and liberate KYNA through aspartate aminotransferase (AspAT) (153, 157, 158). KYNA is readily absorbed from the gut into the bloodstream (155). Interestingly, rats with the probiotic *Bifidobacteria infantis* in the gut have significantly higher KYNA levels in the blood than un-colonized control animals (159). Furthermore, blood from *B. infantis*-colonized animals exhibits a lower TNF induction after *ex vivo* challenge with LPS, which is a typical indication of an endotoxin tolerance. There are also indications that KYNA selectively regulates the growth, and thereby the composition, of the intestinal microbiota (160). In this context, the microbial-mediated KYNA catabolism, known so far from *Pseudomonas* and *Aerococcus* (60, 61), might be relevant. Interestingly, feed supplementation with very high amounts of KYNA might have a toxic/stress-inducing effect in rainbow trout (161). Hence, further studies are necessary to evaluate if a supplementation of KYNA is beneficial or detrimental to human health.

CONCLUSION

Due to the proven relevance of KYNA for various diseases, it is often mooted as both a target and agent for therapeutic interventions. However, the interference of KYNA with diverse immune-related signaling pathways requires further in-depth analysis to avoid unexpected adverse consequences.

AUTHOR CONTRIBUTIONS

EW and JG have contributed equally to this work; they designed the manuscript and approved it for publication. AH and AR contributed to critically revising the paper.

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