Brain, Behavior, and Immunity 111 (2023) 312–319

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Correlations between kynurenines in plasma and CSF, and their relation to markers of Alzheimer's disease pathology

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ARTICLE INFO

Keywords:
Kynurenine pathway
Kynurenines
Plasma
CSF
Alzheimer's disease
Amyloid-beta
Phosphorylated-tau
Neuroprotective
Neurotoxic
Cognitive impairment

ABSTRACT

Introduction: Altered levels of kynurenines in blood and cerebrospinal fluid (CSF) have been reported in Alzheimer's disease (AD). However, it is still largely unknown whether peripheral kynurenine concentrations resemble those found in CSF and how they relate to AD pathology. We therefore studied correlations between kynurenines in plasma and CSF and their associations with CSF amyloid-beta ($A\beta_{1-42}$) and tau levels in patients from the memory clinic spanning the whole cognitive spectrum.

Methods: The Biobank Alzheimer Center Limburg study is a prospective cohort study of consecutive patients referred to the memory clinic of the Alzheimer Center Limburg. Plasma and CSF concentrations of tryptophan (TRP), eight kynurenines and neopterin from 138 patients were determined by means of LC-MS/MS. Additionally, CSF $A\beta_{1-42}$, total-tau (t-tau) and phosphorylated tau (p-tau) concentrations were determined using commercially available single-parameter ELISA methods. Partial correlations were used to analyze cross-sectional associations between kynurenines in plasma and CSF and their relation to AD related CSF-biomarkers adjusted for age, sex, educational level, and kidney function.

Results: Moderate to strong correlations were observed between plasma and CSF levels for quinolinic acid (QA; $r = 0.63$), TRP ($r = 0.47$), anthranilic acid ($r = 0.59$), picolinic acid ($r = 0.55$), and the kynurenine (KYN)/TRP ratio (KTR; $r = 0.55$; all $p < 0.0001$), while other kynurenines correlated only weakly with their corresponding CSF values. No correlations were found between plasma and CSF levels of KA/QA. Several kynurenines were also weakly correlated with $A\beta_{1-42}$, t-tau or p-tau. Plasma levels of KA/QA were negatively correlated with $A\beta_{1-42}$ ($r = -0.21$, $p < 0.05$). Plasma levels of TRP were negatively correlated with t-tau ($r = -0.19$) and levels of KYN with p-tau ($r = -0.18$; both $p < 0.05$). CSF levels of KYN ($r = 0.20$, $p < 0.05$), KA ($r = 0.23$, $p < 0.01$), and KTR ($r = 0.18$, $p < 0.05$) were positively correlated with $A\beta_{1-42}$. Finally, TRP and KYN were negatively ($r = -0.22$ and $r = -0.18$, respectively), and neopterin positively ($r = 0.19$) correlated with p-tau (all $p < 0.05$).

Conclusions: Plasma concentrations of TRP, KP metabolites, KTR, and neopterin all significantly correlated positively with their corresponding CSF concentrations, but many correlations were weak. Additionally, our results suggest a relation between higher kynurenine levels and lower AD pathology load. These results need verification in future studies and require more research into (shared) underlying mechanisms.

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https://doi.org/10.1016/j.bbi.2023.04.015
Received 13 November 2022; Received in revised form 21 March 2023; Accepted 30 April 2023
Available online 4 May 2023

1. Introduction

Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) and tau accumulation, oxidative stress, neuroinflammation and metabolic dysfunction, physiological changes that may be present decades before dementia onset (Jansen et al., 2015; Galasko and Montine, 2010; Jha et al., 2017). However, the exact disease cascade of AD is still not fully understood, and disease-modifying treatment aimed at AD pathology so far has had little to no clinical effects, so that new or additional treatment targets are being investigated (Huang et al., 2020). An interesting modulating pathway is the kynurenine pathway (Fig. 1). Through their role in various (pathological) processes, metabolites of the kynurenine pathway have been associated with a wide range of different disease states, including neurodegenerative diseases, neurological disorders, psychiatric disorders, and chronic diseases such as cancer and cardiovascular diseases (Joisten, 2020; Cervenka et al., 2017; Kincses et al., 2010; Giil et al., 2017; Vécsei et al., 2013; Savitz, 2020).

Studies including post-mortem brain tissue, cell culture models and preclinical animal models suggest that kynurenines play a role in pathophysiological processes associated with AD (Vécsei et al., 2013; Bonda et al., 2010; Guillemin et al., 2005; Rahman et al., 2009; Guillemin, 2005). For instance, kynurenic acid (KA) protects against glutamate mediated excitotoxicity and is considered a neuroprotective metabolite, whereas quinolinic acid (QA) may exert neurotoxicity via different mechanisms, including inhibition of glutamate uptake by astrocytes, mitochondrial dysfunction, free radical production, and immunoregulation (Vécsei et al., 2013; Zwilling et al., 2011; Carrillo-Mora et al., 2010; Guillemin, 2012; Sharma et al., 2018). In several clinical studies, altered levels of kynurenines in blood and cerebrospinal fluid (CSF) have been reported in patients with AD compared to healthy controls (Giil et al., 2017; Gulaj et al., 2010; Jacobs, 2019; Sorgdrager et al., 2019; van der Velpen et al., 2019; Wennstrom, et al., 2014; Whiley et al., 2021; González-Sánchez et al., 2020). Additionally, associations have been observed with $A\beta_{1\text{-}42}$ (Jacobs, 2019; Chatterjee, 2019) and phosphorylated tau (p-tau) in some studies (Jacobs, 2019; Wennstrom, et al., 2014), while others found no associations with $A\beta_{1\text{-}42}$ (van der Velpen et al., 2019; Wennstrom, et al., 2014; González-Sánchez et al., 2020). Indeed, results from clinical studies such as these have been somewhat inconsistent, and most have investigated kynurenines in blood, which is less invasive to obtain compared to CSF.

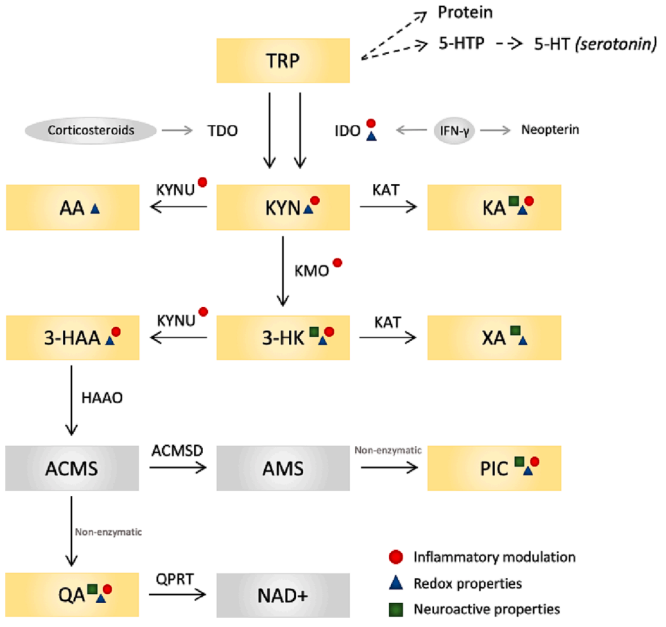

Fig. 1. The kynurenine pathway. Through the kynurenine pathway, tryptophan (TRP) is converted to kynurenine (KYN) by the enzymes tryptophan-2,3-dioxygenase (TDO) and indolamine-2,3-dioxygenase (IDO). TDO depends for a large part on corticosteroids, whereas IDO can be directly upregulated by proinflammatory cytokines, including Interferon-γ (IFN-γ). At the same time, IFN-γ increases neopterin levels, a compound of which its activity is an indication of a pro-inflammatory immune status. KYN can be degraded into more downstream metabolites of the pathway, also called kynurenines, which have neuroactive and immunological properties (measured metabolites in yellow). 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; AA, anthranilic acid; ACMS, 2-amino-3-carboxymuconic-6-semialdehyde; ACMSD, 2-amino-3-carboxymuconate-semialdehyde decarboxylase; AMS, 2-aminomuconic-6-semialdehyde; HAAO, 3-hydroxyanthranilic acid 3,4-dioxygenase; KA, kynurenic acid; KAT, kynurenine transaminase; KYN, kynurenine; KYNU, kynureninase; NAD^+, nicotinamide adenine dinucleotide; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan; XA, xanthurenic acid.

According to a recent review, correlations between blood and CSF levels of some metabolites (e.g. kynurenine (KYN), 3-hydroxykynurenine (3-HK), anthranilic acid (AA), picolinic acid (PIC), and QA showed moderate to strong positive correlations, which were largely consistent across preclinical and human studies, and irrespective of disease status (Skorobogatov et al., 2021). Correlations between levels of other metabolites (e.g. tryptophan (TRP) and KA) were largely weak and inconsistent (Skorobogatov et al., 2021). However, so far, most studies have investigated correlations between blood and CSF levels of TRP and KYN, while studies including downstream metabolites (e.g. 3-HK, xanthurenic acid (XA), AA, 3-hydroxyanthranilic acid (3-HAA), and PIC) are scarce (Jacobs, 2019; Sorgdrager et al., 2019; González-Sánchez et al., 2020; Skorobogatov et al., 2021; Lim, 2017; Heyes et al., 1991; Heyes et al., 1994). Additionally, sample sizes have often been relatively small. As such, it remains to be established whether peripheral kynurenine concentrations in blood resemble those found in CSF and how they relate to AD pathology.

The present study used data from patients from the memory clinic across the full disease severity spectrum, including individuals with subjective cognitive decline (SCD), mild cognitive impairment (MCI) and mild dementia, to investigate correlations between plasma and CSF kynurenine levels and their associations with CSF AD pathology markers $A\beta_{1\text{-}42}$ and tau.

2. Materials and methods

2.1. Study population and design

We used baseline data from 138 patients who participated in the Biobank Alzheimer Center Limburg (BBACL) study between 2009 and 2019 and for whom kynurenines in plasma and matched CSF samples were quantified in June 2019. The BBACL study is an ongoing prospective cohort study in patients with cognitive complaints who are referred to the memory clinic of the Alzheimer Center Limburg, Maastricht University Medical Center+ (MUMC+), the Netherlands. Inclusion criteria at baseline were a Mini Mental State Examination score of $\geq$ 20 and a Clinical Dementia Rating scale score of 0–1 (Morris, 1993; Folstein et al., 1975). Exclusion criteria were a preexisting psychiatric diagnosis (schizophrenia, bipolar disorder or a current major depressive disorder), alcohol induced cognitive problems, the presence of a medical disorder which could result in cognitive impairment (Normal Pressure Hydrocephalus, Huntington's disease, a recent transient ischemic attack or cerebrovascular accident (within 2 years, or cognitive decline within 3 months), epilepsy, brain tumor, encephalitis), and the absence of a reliable informant. At baseline, all patients underwent neuropsychological and cognitive evaluation, physical examination, a magnetic resonance imaging (MRI) of the brain and collection of blood samples. Collection of cerebrospinal fluid (CSF) was optional and done only if applicable for clinical diagnostic purposes. A clinical diagnosis was made by a multidisciplinary team. A dementia diagnosis was made according to DSM IV or DSM 5 criteria (APA). All patients gave written informed consent to participate in the study. The Medical Ethics Review

Committee of MUMC+ provided ethical approval for the BBACL study (METC 15–4-100, 09–3-037, and 09–3-037).

2.2. Blood and CSF collection, biochemical analysis

Processing and storage of plasma samples was done according to harmonized standard operating procedures at the Biobank Maastricht, the ISO (9001–2015) certificated Biobank of the MUMC+. Venous non-fasting blood samples (8 ml) were collected in EDTA-tubes, then centrifuged at 4°C at 2000g for 10 min, aliquoted into 0.5 ml vials and stored at −80°C in the Biobank until analysis.

CSF was collected for diagnostic purposes by lumbar puncture at intervertebral space level L3/L4 or L4/L5, centrifuged at 2000g for 10 min, and aliquoted into 0.5 ml polypropylene tubes. CSF markers of $A\beta_{1-42}$, total-tau (t-tau), and phosphorylated tau (p-tau) were determined at the department of Neurochemistry, Radboud University Medical Center, Nijmegen, the Netherlands, using commercially available single-parameter ELISA methods (respectively Innotest® $A\beta_{1-42}$ and Innotest® hTAU-Ag; Innogenetics, Ghent, Belgium).

Plasma and CSF concentrations of TRP, eight kynurenines (KYN, 3-HK, KA, XA, AA, 3-HAA, PIC, and QA) and neopterin were determined by Bevital AS, Bergen, Norway, using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Additionally, ratios were calculated of KA/QA (neuroprotective/ neurotoxic ratio) and of KTR (KYN/TRP*1000) as an indicator of IDO activity, one of the enzymes responsible for conversion of TRP into KYN.

CSF concentrations of XA (all) and 3-HAA (n = 40) were below limits of detection. For 3-HAA, CSF-concentrations of these 40 patients were winsorized at the lowest observed value (i.e. 1.01 nM).

Plasma riboflavin (B2 vitamer), PLP (B6 vitamer), and creatinine were determined in the same aliquot as used for kynurenine measurements. From creatinine levels, the glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology collaboration equation (CKD-EPI; ml/min/1.73 m^2) (Levey et al., 2009).

2.3. Statistical analysis

Statistical analyses were performed with STATA version 17 for MacOS. Differences in baseline demographics and clinical characteristics between patients with SCD, MCI and dementia were investigated using ANOVA, chi^2 and Kruskall-Wallis tests where appropriate. Differences in kynurenine levels across these diagnostic groups were investigated using ANCOVA, while controlling for age, sex, educational level, and eGFR. Next, partial correlation analyses were done to investigate correlations between kynurenine concentrations in plasma and CSF, and between kynurenine concentrations and CSF levels of $A\beta_{1-42}$, t-tau and p-tau, while controlling for age, sex, educational level, and eGFR. Additionally, analyses were repeated using Spearman rank correlations (rho). Pre-specified sensitivity analyses were done in which analyses were restricted to individuals with none to mild kidney damage (eGFR ≥ 60). Except for TRP and KA/QA in plasma, all metabolites and AD biomarkers were log-transformed prior to analysis.

3. Results

3.1. Clinical characteristics of individuals with SCD, MCI or dementia

The 138 patients in the study (68.1% men) had a mean (SD) age of 63.4 (8.5) years and included 66 patients with SCD (47.8%), 47 with MCI (34.1%) and 24 with dementia (17.4%). For one individual, information about the diagnosis was missing. Of individuals with dementia, 18 (75%) had probable AD.

Compared to the group with SCD, those with dementia or MCI were older (both $p < 0.001$), had lower MMSE scores ($p < 0.001$ and $p = 0.008$, respectively), lower levels of $A\beta_{1-42}$ ($p < 0.001$ and $p = 0.017$, respectively), and higher levels of t-tau and p-tau (all $p < 0.001$; Table 1). Patients with dementia were more often women compared to patients with SCD ($p = 0.013$). Patients with dementia also had lower MMSE scores, higher levels of t-tau and p-tau (Table 1), and lower 3-HAA levels in CSF (Table 2) compared to patients with MCI ($p < 0.001$, $p = 0.004$, $p = 0.004$, and $p = 0.020$, respectively). No other kynurenine metabolite or ratio showed significant differences between groups.

3.2. Correlations between kynurenines in plasma and CSF.

Plasma concentrations of TRP, kynurenines, KTR, and neopterin were all positively correlated with their corresponding CSF levels, after controlling for age, sex, educational level, and eGFR (Table 3). Strong correlations were observed for QA and moderate correlations for TRP, AA, PIC, and KTR. In contrast, plasma concentrations of KYN, 3-HK, KA, 3-HAA, and neopterin correlated weakly with their corresponding CSF values, and no correlations were found between plasma and CSF levels of KA/QA.

In sensitivity analyses, these results were not altered by restricting analyses to patients with none to mild kidney damage (eGFR ≥ 60; Table S4). Results were also similar to those obtained in non-parametric correlation analyses (Table S5). As stated before, CSF levels for XA were below the level of detection and hence correlations with plasma levels could not be computed. For full correlation patterns between all metabolites in CSF and plasma see supplementary Fig. 1.

3.3. Correlations between kynurenine concentrations and CSF $A\beta_{1-42}$, p-tau and t-tau.

Several metabolites were also weakly correlated with AD pathological markers, after controlling for age, sex, educational level, and kidney

Table 1
Baseline characteristics of study population by clinical diagnosis.

	SCD (n = 66)	MCI (n = 47)	Dementia (n = 24)	P *value*
Demographics				
Age (in years)	60.4 ± 8.6	65.8 ± 8.0[b]	67.2 ± 6.4[a]	< **0.001**
Men	51 (77.3)	31 (66.0)	12 (50.0)[a]	**0.038**
Educational level				0.514
Low	20 (30.3)	10 (21.3)	9 (37.5)	
Intermediate	32 (48.5)	23 (48.9)	10 (41.7)	
High	14 (21.2)	14 (29.8)	5 (20.8)	
eGFR (ml/min/ 1.73 m2)	86.0 ± 11.8	80.5 ± 14.4	82.1 ± 11.1	0.149
MMSE (mean score)	28.5 ± 1.4	27.7 ± 1.8[b]	25.2 ± 2.5[a,c]	< **0.001**
B-vitamins				
PLP, nM	47.7 [33.6–68.3]	47.0 [31.2–79.3]	57.3 [36.9–76.3]	0.511
Riboflavin, nM	12.3 [7.3–19.5]	13.8 [7.9–19.6]	13.7 [6.3–18.1]	0.801
CSF Biomarkers				
$A\beta_{1-42}$, ng/L	1096 [868–1337]	785 [577–1272][b]	702 [545–873][a]	**0.001**
t-tau, ng/L	203 [154–276]	347 [247–589][b]	504 [414–899][a,c]	< **0.001**
p-tau, ng/L	47 [35–54]	55 [47–85][b]	84 [68–109][a,c]	< **0.001**

Data are means ± SD or n (%) for the demographics and presented as median [IQR] for B vitamers and CSF biomarkers. Difference between groups were investigated with ANOVA, Chi^2 and Kruskal-Wallis tests where appropriate. CSF biomarkers were available for 135 individuals (SCD: 66, MCI: 46, dementia: 23). Abbreviations: SCD, subjective cognitive decline; MCI, mild cognitive impairment; eGFR, glomerular filtration rate; MMSE, mini mental state examination; PLP, pyridoxal phosphate.

[a] Dementia versus SCD.
[b] MCI versus SCD.
[c] Dementia versus MCI.

Table 2
Metabolite concentrations by clinical diagnosis.

	Plasma				CSF			
	SCD	MCI	Dementia	*p value*	SCD	MCI	Dementia	*p value*
TRP, μM	62.1 [56.6–69.5]	61.9 [49.0–69.8]	59.7 [50.4–66.2]	0.260	2.7 [2.5–3.1]	2.7 [2.4–3.2]	2.6 [2.4–3.0]	0.767
KYN, μM	1.57 [1.40–1.78]	1.66 [1.48–2.02]	1.58 [1.38–1.87]	0.229	0.05 [0.04–0.06]	0.06 [0.04–0.08]	0.06 [0.05–0.08]	0.610
3-HK, nM	41.9 [36.5–49.8]	44.7 [37.3–57.2]	45.8 [33.0–51.1]	0.696	5.1 [3.8–6.5]	5.3 [3.9–6.4]	4.4 [3.7–5.2]	0.094
KA, nM	42.6 [35.2–54.5]	48.7 [32.9–59.8]	47.3 [40.0–53.6]	0.574	2.1 [1.5–3.4]	2.2 [1.6–3.6]	2.2 [1.5–3.2]	0.389
XA, nM	14.4 [10.7–21.1]	14.9 [10.2–21.2]	14.7 [10.7–19.6]	0.447	–	–	–	–
AA, nM	12.1 [10.3–15.3]	14.3 [11.2–18.4]	14.0 [12.1–16.4]	0.330	4.3 [3.6–5.3]	5.0 [3.7–5.8]	4.6 [4.1–5.0]	0.405
3-HAA, nM	41.1 [33.3–54.6]	40.9 [31.5–56.3]	35.6 [28.3–51.6]	0.828	1.2 [1.0–1.5]	1.5 [1.1–1.8]	1.1 [1.0–1.6][c]	**0.037**
PIC, nM	46.2 [36.1–61.6]	46.9 [35.5–57.8]	46.6 [34.3–62.0]	0.452	20.8 [16.9–27.6]	21.4 [17.8–29.3]	20.4 [15.3–26.6]	0.940
QA, nM	381 [326–465]	379 [318–503]	380 [322–414]	0.510	29.0 [21.5–39.3]	31.8 [25.7–46.9]	28.8 [21.8–33.8]	0.218
KA/QA	0.12 [0.10–0.14]	0.12 [0.09–0.14]	0.13 [0.10–0.14]	0.443	0.08 [0.05–0.11]	0.07 [0.05–0.10]	0.07 [0.06–0.12]	0.305
KTR	25.0 [22.3–29.1]	26.8 [23.8–31.5]	27.2 [24.0–30.9]	0.458	18.5 [16.3–23.3]	20.2 [15.3–26.8]	21.2 [17.8–26.0]	0.536
Neopterin, nM	17.1 [14.8–22.4]	18.6 [14.7–23.2]	19.2 [15.7–23.4]	0.858	18.0 [14.9–23.1]	18.6 [14.9–23.5]	21.2 [18.4–24.9]	0.333

Data are presented as median [IQR]. Difference between groups were investigated with ANCOVA, while controlling for age, sex, educational level and eGFR. Except for TRP and KA/QA in plasma, all metabolites were log-transformed prior to analysis. SCD, subjective cognitive decline; MCI, mild cognitive impairment; 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; AA, anthranilic acid; KA, kynurenic acid; KTR, kynurenine/tryptophan ratio; KYN, kynurenine; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan; XA, xanthurenic acid.
[c] Dementia versus MCI.

Table 3
Partial correlations between kynurenine levels in plasma and CSF.

Metabolite	*r*	*p*
TRP	**0.47**	**< 0.001**
KYN	**0.37**	**< 0.001**
3-HK	**0.20**	**0.024**
KA	**0.19**	**0.031**
AA	**0.59**	**< 0.001**
3-HAA	**0.23**	**0.009**
PIC	**0.55**	**< 0.001**
QA	**0.63**	**< 0.001**
KA/QA	0.12	0.154
KTR	**0.55**	**< 0.001**
Neopterin	**0.25**	**0.005**

Analyses were controlled for age, sex and educational level. Except for TRP and KA/QA in plasma, all metabolites were log-transformed.
3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; AA, anthranilic acid; KA, kynurenic acid; KTR, kynurenine/tryptophan ratio; KYN, kynurenine; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan.

function (Table 4). Plasma levels of KA/QA were negatively correlated with CSF $A\beta_{1\text{-}42}$. Additionally, plasma levels of TRP were negatively correlated with t-tau and KYN was negatively correlated with CSF p-tau.

With respect to CSF, levels of KYN, KA, and KTR were all positively correlated with $A\beta_{1\text{-}42}$. Additionally, TRP and KYN were both negatively, and neopterin positively, correlated with p-tau. Although not all correlations reached statistical significance, these results were similar after restricting analyses to patients with none to mild kidney damage (eGFR $\geq$ 60; Table S6).

4. Discussion

We studied correlations between plasma and CSF kynurenine concentrations and their associations with CSF $A\beta_{1\text{-}42}$ and tau levels in patients from the memory clinic spanning the whole cognitive spectrum from SCD to dementia. Plasma concentrations of TRP, kynurenines, KTR, and neopterin were all positively correlated with their corresponding CSF concentrations. Additionally, several kynurenines were also statistically significant but weakly correlated with AD CSF-markers $A\beta_{1\text{-}42}$, t-tau or p-tau.

4.1. TRP and kynurenines in plasma are positively correlated with their corresponding CSF levels

We found moderate correlations for plasma TRP, AA, PIC, and KTR levels, and weaker plasma correlations of KYN, 3-HK, KA, and 3-HAA with their corresponding CSF values. These findings are partly in line with the traditional view based on *in vivo* studies investigating (transporter-mediated) brain uptake of TRP and kynurenine metabolites (Fig. 2). According to this view, TRP and KYN, and to a lesser degree 3-HK, cross the blood–brain barrier (BBB) by large neutral amino acid transporters (LNAAs), whereas AA enters the brain by passive diffusion (Fukui et al., 1991; Schwarcz et al., 2012). Under normal physiological circumstances, activation of IDO and TDO, two rate-limiting enzymes that catalyze TRP in the brain, is low, and CSF levels of TRP, KYN, 3-HK, and AA are therefore largely dependent on concentrations in the periphery. Studies suggest that 60–78% of KYN in the brain is derived from peripheral sources (Gal and Sherman, 1980; Kita et al., 2002). Transportation of other metabolites, including KA, QA, and 3-HAA, is believed to be limited, and their central concentrations would mainly depend on local synthesis by astrocytes and microglia (Schwarcz et al., 2012; Kitt and Spector, 1987).

However, although *in vivo* studies suggest that QA is not actively transported over the BBB and enters the brain via passive diffusion in negligible amounts (Kitt and Spector, 1987; Foster et al., 1984), QA showed the strongest correlations between plasma and CSF in our study. In rodents, strong correlations were found after immune stimulation as well, both between blood and CSF ($r = 0.97$) (Saito et al., 1993) and between blood and post-mortem brain tissue ($r = 0.83$) (Verdonk et al., 2019). Additionally, in gerbils, 70% of subcutaneously infused QA entered the CSF and 38–49% entered the brain (Heyes and Morrison, 1997). Similarly, moderate to strong positive correlations between blood and CSF have been reported in patients with neurodegenerative diseases (Sorgdrager et al., 2019), psychiatric disorders (Haroon et al., 2020), and other illnesses associated with an elevated inflammatory status (Lim, 2017; Heyes et al., 1991; Heyes et al., 1994; Valle, 2004; Raison, 2010), whereas no significant correlations between plasma and CSF were reported in a study investigating healthy individuals (Isung et al., 2021). These results suggest that diagnosis-associated biological processes such as inflammation and a decreased integrity of the BBB might play a role in these strong correlations (Savitz, 2020) and explain the correlation in our clinical population. This is indeed in line with a recent report of a clinical study (Sorgdrager et al., 2019), including patients with AD dementia ($n = 33$), Parkinson's disease ($n = 33$), and healthy controls ($n = 39$). In this study, concentrations of all determined

Table 4
Partial correlations between kynurenines in plasma and CSF and AD pathological markers in CSF.

		$A\beta_{1\text{-}42}$	t-tau	p-tau			$A\beta_{1\text{-}42}$	t-tau	p-tau
Plasma					*CSF*				
TRP	M1	−0.13	−0.16	−0.11	TRP	M1	0.04	−0.16	**−0.22***
	M2	−0.11	**−0.19***	−0.13		M2	0.04	−0.16	**−0.22***
KYN	M1	0.11	**−0.19***	**−0.21***	KYN	M1	**0.23****	−0.12	**−0.20***
	M2	0.07	−0.14	**−0.18***		M2	**0.20***	−0.08	**−0.18***
3-HK	M1	0.11	0.01	−0.01	3-HK	M1	0.16	−0.04	−0.01
	M2	0.05	0.10	0.05		M2	0.15	−0.03	0.00
KA	M1	−0.01	−0.09	−0.15	KA	M1	**0.25****	0.01	−0.07
	M2	−0.09	−0.00	−0.10		M2	**0.23****	0.05	−0.05
XA	M1	−0.11	−0.04	−0.03	XA	M1	–	–	–
	M2	−0.14	−0.01	−0.01		M2	–	–	–
AA	M1	0.08	−0.08	−0.16	AA	M1	0.10	−0.05	−0.17
	M2	0.03	−0.02	−0.12		M2	0.06	−0.00	−0.14
3-HAA	M1	−0.06	−0.15	−0.15	3-HAA	M1	0.05	−0.12	−0.10
	M2	−0.08	−0.13	−0.14		M2	0.04	−0.10	−0.08
PIC	M1	−0.12	0.01	0.08	PIC	M1	0.01	0.02	0.10
	M2	−0.10	−0.01	0.07		M2	0.02	0.02	0.10
QA	M1	**0.22***	−0.11	−0.12	QA	M1	**0.18***	−0.10	−0.16
	M2	0.16	0.00	−0.06		M2	0.13	−0.03	−0.12
KA/QA	M1	**−0.22***	−0.01	−0.07	KA/QA	M1	0.12	0.08	0.04
	M2	**−0.21***	−0.02	−0.08		M2	0.13	0.07	0.03
KTR	M1	**0.22***	−0.00	−0.05	KTR	M1	**0.21***	−0.02	−0.06
	M2	0.17	0.08	0.00		M2	**0.18***	−0.02	−0.04
Neopterin	M1	0.09	0.06	0.01	Neopterin	M1	0.04	0.17	**0.19***
	M2	0.06	0.11	0.04		M2	0.05	0.16	**0.19***

Analyses were controlled for age, sex and educational level in the first model (M1). Additionally, analyses were controlled for eGFR in main model 2 (M2). Except for TRP and KA/QA in plasma, all metabolites were log-transformed.
3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; AA, anthranilic acid; KA, kynurenic acid; KTR, kynurenine/tryptophan ratio; KYN, kynurenine; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan; XA, xanthurenic acid. *P < 0.05, **P < 0.01, ***P < 0.001.

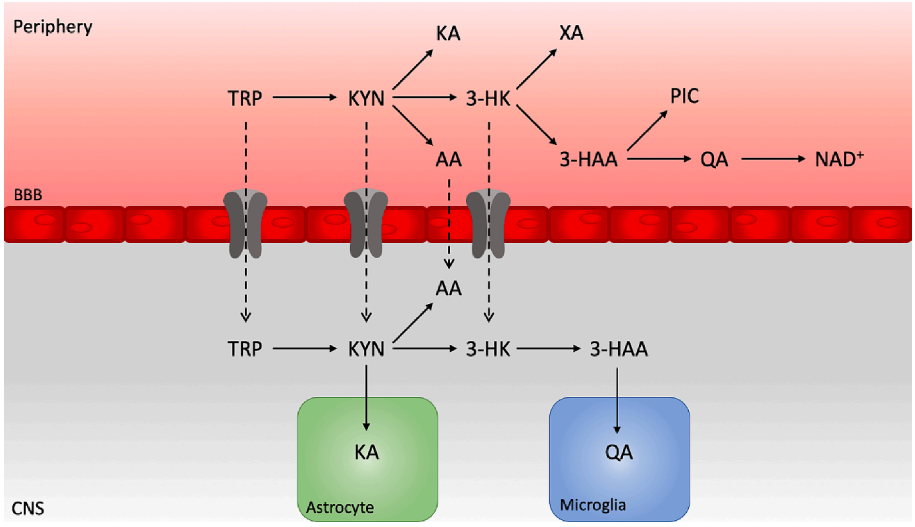

Fig 2. Passage of kynurenines through the blood–brain barrier. 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; AA, anthranilic acid; KA, kynurenic acid; KYN, kynurenine; NAD^+, nicotinamide adenine dinucleotide; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan; XA, xanthurenic acid.

kynurenines (KYN, 3-HK, KA, XA) in serum, and of QA in particular, were positively associated with their corresponding levels in CSF (Sorgdrager et al., 2019). Yet, in another clinical study including a smaller sample of 20 patients with AD and 18 healthy controls, positive correlations were found between plasma and CSF levels for KYN, 3-HK, AA, PIC and KTR, but not for TRP, KA, 3-HAA and QA (Jacobs, 2019). One reason for these differences might be attributed to the larger size of matched samples in our study.

4.2. CSF levels of KTR are associated with higher CSF levels of $A\beta_{1\text{-}42}$

CSF levels of KTR (as a proxy for IDO activity) were associated with higher levels of $A\beta_{1\text{-}42}$, which is indicative of a lower degree of plaque aggregation in the brain (Blennow et al., 2010). In plasma, a similar but non-significant trend was found. Similarly, QA was not significantly correlated with $A\beta_{1\text{-}42}$ after controlling for kidney function but showed a tendency for a positive correlation as well. These results were consistent for plasma and CSF and contrast with previous studies that suggest a promoting role for IDO and QA in pathophysiological processes associated with AD (Bonda et al., 2010; Guillemin et al., 2005; Guillemin, 2005). For instance, immunochemical studies suggest that expression of IDO-1 and QA is increased in the brains of patients with AD pathology (Bonda et al., 2010) or AD dementia (Guillemin et al., 2005) compared to controls and is highest around senile plaques (Guillemin et al., 2005; Guillemin, 2005). Additionally, IDO-1 has been found to be co-localized alongside neurofibrillary tangles (Bonda et al., 2010), and in primary

cultures of human neurons that were incubated with QA concentrations of 50–1200 nM, tau phosphorylation increased in a dose dependent manner (Rahman et al., 2009), although these concentrations are higher than those typically reported in the CSF of patients with neurodegenerative disorders (Jacobs, 2019; Sorgdrager et al., 2019; Janssens et al., 2020). QA has been known for its potent neurotoxic effects through its role as a NMDA receptor agonist (Sharma et al., 2018), but has been associated with other pathological mechanisms as well, including neuroinflammation and oxidative stress (Guillemin, 2012).

At the same time, results from clinical studies investigating QA and KTR levels in individuals with AD have been inconsistent, with most studies reporting no significant differences in CSF or blood (Jacobs, 2019; Sorgdrager et al., 2019; Whiley et al., 2021) and others reporting even lower peripheral levels of QA (Giil et al., 2017) compared to controls. Interestingly, according to a recent study, plasma levels of QA were lower in individuals who progressed from cognitively normal to MCI or from MCI to AD, compared to cognitively normal individuals that did not progress (Cespedes, 2022). Studies investigating levels in whole brain sections of several different regions did not find significant differences (Mourdian et al., 1989). Additionally, although previous studies investigating associations between kynurenines and AD pathological markers were smaller (n = 38–74), associations were not significant between CSF levels of $A\beta_{42}$ and CSF levels of QA (Jacobs, 2019; van der Velpen et al., 2019) or KTR (Jacobs, 2019), nor between these metabolites and p-tau or t-tau (Jacobs, 2019). These mixed findings are interesting, given the supposed neurotoxic properties of QA. However, levels of QA in blood and CSF and their associations with pathological markers might not be accurate reflections of QA's concentration in diseased versus unaffected regions in the brain. Additionally, endogenous levels of QA might be too low to influence AD pathology. Nevertheless, it remains unclear why we found a positive trend with levels of $A\beta_{1\text{-}42}$, which should be verified in future studies.

4.3. KA and KYN in CSF are associated with higher CSF levels of $A\beta_{1\text{-}42}$

Interestingly, CSF levels of KA, and of its precursor KYN, were also positively associated with $A\beta_{1\text{-}42}$, and they remained significant after additionally adjusting for kidney function. KA contains anti-glutamatergic properties and has been put forward as a neuroprotective metabolite by its potential to inhibit glutamate induced excitotoxicity, one of the neurodegenerative processes associated with AD (Sharma et al., 2018). In preclinical animal models, KA has elicited neuroprotective effects. For instance, increasing KA levels in the brain prevented synaptic loss and spatial memory deficits in a transgenic mouse model of AD (Zwilling et al., 2011). Similarly, increasing KA levels by systemic administration of KYN decreased cell damage and improved spatial memory in rats after intrahippocampal injection of Aβ (Carrillo-Mora et al., 2010). In clinical studies investigating KA in CSF of AD patients, higher levels of KA have generally been reported (Jacobs, 2019; van der Velpen et al., 2019; González-Sánchez et al., 2020). Additionally, in a previous community-based study from our group, we showed that KA was associated with lower odds of cognitive impairment and with better executive functioning and attention (Bakker et al., 2021). These results suggest that KA might be upregulated in response to neurogenerative processes and point towards a neuroprotective role.

In addition to associations with $A\beta_{1\text{-}42}$, KYN levels, both in plasma and CSF, were also negatively associated with p-tau. Soluble and highly phosphorylated tau species are closely associated with synaptic dysfunction and cell loss and are commonly used in clinical diagnostics (Berger et al., 2007; Ittner, 2010; Rocher et al., 2010; SantaCruz et al., 2005). KYN is believed to be an immunomodulator and its levels in plasma were also negatively correlated with p-tau in a previous study in AD patients (Jacobs, 2019), although its potential role in AD pathology is not sufficiently clear. Studies investigating its levels in AD patients generally report no differences compared to healthy controls (Gulaj et al., 2010; Jacobs, 2019; Sorgdrager et al., 2019; van der Velpen et al., 2019). Similarly, KYN levels were not associated with cognitive functioning in patients with AD (Gulaj et al., 2010; Whiley et al., 2021) or in community-dwelling older adults (Solvang et al., 2019). As such, more research is needed, investigating associations of these and other kynurenines with pathological markers.

4.4. Strengths and limitations

Strengths of the present study consist of a relatively large naturalistic cohort of memory clinic patients across the full cognitive spectrum, together with plasma and CSF matched samples. Additionally, in the BBACL study, a comprehensive profile of plasma kynurenines was determined, together with creatinine concentrations which allowed to control for kidney function. One limitation is that samples were non-fasting. Additionally, CSF samples were collected among participants that were generally younger and cognitively healthier, indicating selection bias in this study. Another limitation is that we were unable to investigate sex-specific differences across subgroups because these type of analyses ask for larger cohorts. Previous studies suggest that kynurenine metabolism is generally lower in women (Darst et al., 2019; Theofylaktopoulou et al., 2013). Indeed, we observed that in the group with SCD, plasma levels of 3-HAA and CSF levels of QA were lower in women (data not shown). With respect to the group with MCI, plasma levels of KA, XA, AA, 3-HAA, and QA were all lower in women, as were CSF levels of AA. Lastly, in the group with dementia, CSF levels of QA were lower in women as well. Future studies should investigate these sex-specific findings and other differences across subgroups in larger cohorts in order to study putative effect modification with sufficient statistical power.

We were also unable to control analyses for diet (Holthuijsen et al., 2022; Li et al., 2021) and physical activity (Joisten, 2020; Schlittler et al., 2016), which are lifestyle factors that potentially affect peripheral concentrations of kynurenines. For instance, in a study in Colorectal cancer survivors, a healthy diet (according to recommendations by the World Cancer Research Fund/ American Institute for Cancer Research and Dutch Healthy Diet) was associated with lower levels of 3-HK and QA and higher levels of KA and PIC (Holthuijsen et al., 2022), whereas in another study, in community-dwelling adults, a healthier (Mediterranean) diet was associated with lower concentrations of all measured kynurenines (KYN, 3-HK, KA, AA, 3-HAA, QA) (Li et al., 2021). With respect to physical activity, blood levels of KA and QA increased after endurance exercise (Joisten, 2020; Schlittler et al., 2016). More research is needed into these lifestyle factors as potential ways to regulate concentrations of KA and other metabolites in such a way that optimal concentrations are established. By design, we also excluded patients with severe cognitive complaints (MMSE < 20), which limits generalizability to patients with moderate to severe dementia.

4.5. Conclusion

Our study showed that plasma concentrations of TRP, KP metabolites, KTR, and neopterin all significantly correlated positively with their corresponding CSF concentrations in a population of middle-aged to older adults from a memory clinic setting. Additionally, our results suggest a relation between higher kynurenine levels and lower AD pathology load. These results need verification in future studies and require more research into (shared) underlying mechanisms.

Declaration of Competing Interest

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.

Data availability

Data will be made available on request.

Acknowledgements

The infrastructure of the research in this paper was partly funded by the Dutch Federation of University Medical Centers (Parelsnoer Institute). The authors would like to thank all participants and all staff of the BBACL study, in particular Nico Rozendaal and Ron Mengelers for their work in data management and Tanja Hameleers, Carla Meesters, and Astrid Quist for their contribution in study coordination and data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.04.015.

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