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Review Paper

Dynamic Changes in Metabolites of the Kynurenine Pathway in Alzheimer's Disease, and Huntington's Disease: A Systematic Review of Pre-clinical Studies

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Running Title KP in Alzheimer and Huntington Diseases

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ABSTRACT

Background: Alterations in the kynurenine pathway (KP) metabolite can contribute to the pathogenesis and progression of many psychiatric and neurodegenerative illnesses, including Alzheimer disease (AD) and Huntington disease (HD), primarily through neuroinflammatory pathways and generating neurotoxic metabolites.

Objectives: This systematic review highlights the evidence obtained by in vivo animal studies on alterations in KP metabolites and enzymes in AD and HD.

Materials & Methods: We searched PubMed, Scopus, Web of Science, and EMBASE databases

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from the beginning of 2000 to January 2024 and included English-language in vivo articles comparing levels of KP metabolites or enzymes in rats or mice AD or HD models with controls.

Results: A total of 19 studies, comprising 93 experimental and 95 control animals, were included. In AD models compared to controls, the following changes were reported: higher levels of tryptophan (TRP) in blood; higher kynurenine (KYN) levels in the cortex, hippocampus, hypothalamus, and prefrontal cortex; higher quinolinic acid (QUIN) levels in the hippocampus and cerebrum; higher indoleamine 2,3-dioxygenases levels in the cerebrum, prefrontal cortex, and hippocampus; and a higher KYN/TRP ratio in the hippocampus, cortex, and cerebellum. Reports on HD models compared to controls showed higher 3-hydroxykynurenine levels in the striatum and cortex and lowered TRP levels in the striatum.

Conclusion: According to the primary outcomes, KP alterations may lead to the progression of AD and HD. These two diseases can also change the KP pathway factors. Here, we highlighted that changes in the KP metabolites and enzyme levels can help diagnose and treat these diseases.

Keywords: Kynurenine (KYN), Alzheimer disease (AD), Huntington disease (HD), Tryptophan (TRP)

Highlights

- Alterations in the kynurenine pathway (KP) metabolite can play a role in the pathogenesis of Alzheimer disease (AD) and Huntington disease (HD).
- In AD models, kynurenine levels are higher in the cortex, hippocampus, hypothalamus, and prefrontal cortex.
- AD models have higher tryptophan (TRP) levels in their blood.
- The blood of AD models demonstrate higher levels of quinolinic acid (QUIN) in the hippocampal and cerebellum.
- It is reported that AD model blood levels of indoleamine 2,3-dioxygenases are higher in the cerebrum, prefrontal cortex, and hippocampus.
- The striatum and cortex of AD models show higher 3-hydroxykynurenine levels and lower TRP levels than controls.

Introduction

Tryptophan (TRP) is a vital amino acid, a precursor compound to some neuroactive metabolites. This amino acid is a crucial building block of proteins; however, its endogenous metabolism produces various other bioactive compounds. Metabolism of TRP involves two main pathways: 1) The methoxyindole pathway, which produces 5-hydroxytryptamine (5-HT, serotonin) and melatonin, and 2) The kynurenine pathway (KP), which produces kynurenine (KYN) metabolites. KP in the metabolism of TRP is an endogenous immunosuppressive system involved in inflammation control and long-term immune tolerance in numerous organs throughout the body [1]. TRPis mainly metabolized through the latter pathway, in which TRPis converted to N-formylkynurenine either by TRP2,3-dioxygenase (TDO2) or indoleamine 2,3-dioxygenases (IDO-1 and IDO-2) resulting in the production of L-kynurenine (L-KYN). However, L-KYN is then metabolized through one of three routes that produce other metabolites: 1) Neurotoxic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN), initiated by the enzyme KYN monooxygenase (KMO); 2) A neuroprotective metabolite, kynurenic acid (KYNA), via deamination of L-KYN by KYN aminotransferase (KAT); and 3) Anthranilic acid generated by kynureninase [2].

Various etiological hypotheses contributing to the pathogenesis of AD have been suggested, including the generation of neurofibrillary tangles and amyloid beta (Aβ)-containing plaques, dysregulation of the neurotransmitter system and neuroactive metabolites, oxidative stress, and neuroinflammation [3-5]. In AD, cognitive impairment is the most prominent symptom, whereas patients with Huntington disease (HD) display

psychiatric symptoms and motor impairments in addition to cognitive dysfunction [6].

An expansion in the CAG trinucleotide repeat in the Huntingtin gene code region causes AD, a neurological disorder caused which follows an autosomal dominant inheritance pattern. The clinical features of HD include chorea, which usually begins early, cognitive decline, and psychiatric symptoms [7]. The mechanisms of HD pathogenesis are not entirely understood, but they likely include impairment of glial cell function [8], neuroinflammation [9], oxidative stress, and dysregulation of neuroactive metabolites, such as TRP derivatives [10, 11]. Neuroactive metabolites contribute to the pathogenesis of psychiatric and neurodegenerative disorders through various mechanisms, such as excitotoxicity, induction of mitochondrial injury, inflammation, and production of reactive oxygen species (ROS) [12].

Alterations in KP metabolites have been observed in various psychiatric and neurodegenerative diseases, including AD and HD, suggesting the potential role of these metabolites in the pathogenesis of these disorders. However, the exact contributions of disrupted KP to these diseases' pathogenesis have remained to be elucidated [13]. It has been suggested that a shift in KP towards producing neurotoxic metabolites such as QUIN and 3-HK, along with a relative deficiency of KYNA, may promote neurodegeneration. In addition, imbalances in this pathway may contribute to the development and progression of neurodegenerative diseases through various other mechanisms, such as the induction of neuroinflammation and the production of ROS [14].

Considering the KP contribution to neuroinflammation, ROS production, and neurotoxicity production, treatments that inhibit the neurotoxic QUIN-producing part of the KP and stimulate KYNA generation might have therapeutic benefits for patients living with neurodegenerative diseases like AD and HD. In this regard, recent studies have focused on inhibiting certain KP enzymes, including KMO, and the development of KYNA analogs capable of crossing the blood-brain barrier [10, 15, 16].

The extract pathogenesis and molecular pathways involved in neurological disorders have not yet been discovered. So, discovering their pathogenesis is critical to diagnosing, treating, and especially curing these disorders. In this regard, preclinical studies have a significant role, as one of their purposes is to investigate pathways involved in diseases [17].

In this review, we systematically review the published studies using animal models of AD and HD to identify changes to KYN metabolite levels and KP metabolite ratios observed in vivo.

Materials and Methods

This paper has been conducted considering the PRISMA (the preferred reporting items for systematic reviews and meta-analysis, 2020) guidelines [18].

Search strategy and screening

Two authors (Kimia Eyvani and Arian Tavasol) systematically searched online databases, including PubMed, Scopus, Web of Science, and EMBASE, from the beginning of 2000 to January 2024. Their disagreements were resolved by consulting a third author (Milad Alipour). We used the following keywords: "Kynurenine pathway," "tryptophan," "kynurenine," "kynurenic acid," "hydroxytryptamine," "quinolinic acid," "indoleamine 2,3-dioxygenases", "hydroxykynurenine," "TRP 2,3-dioxygenase", "kynurenine monooxygenase," and "kynurenine aminotransferase" combined with either "Alzheimer's disease" or "Huntington's disease" in our search strategy. Also, Arian Tavasol searched Google Scholar as grey literature for further eligible studies. In addition, AT reviewed the reference list of the relevant papers to prevent any eligible study from being missed. We imported all searched papers into the Endnote software for screening. Finally, 19 studies were eligible and included in the systematic review.

Inclusion and exclusion criteria

We included studies according to the following criteria: 1) Observational in vivo studies; 2) Studies conducted on mice, rats, or *Drosophila*; 3) Those that measured the levels of KP metabolites or enzymes in the brain tissue, blood, or urine of the animals; and 4) Studies that reported those levels in AD or HD models and control group. We excluded interventional studies, review articles, letters, non-English articles, and studies without a control group.

Data extraction

Two authors (Arian Tavasol and Kimia Eyvani) conducted data extraction in a structured form. The extracted data were the first author's name, the country where the study was performed, the type of experimental group, the number of experimental animals and controls, age, sample source, experimental design, method of measur-

ing KP metabolites or enzymes, and the levels of KP metabolites or enzymes in experimental group and controls.

Quality assessment

Systematic Review Centre for Laboratory Animal Experimentation's Risk of Bias (SYRCLES) checklist was applied for quality assessment, which evaluates sources of bias, including selection, performance, detection, attrition, and reporting biases [19] (Figure 1).

Results

Study selection

Initially, 1206 studies were identified through a systematic search. After excluding duplicated articles, 893 relevant studies were remained. The titles and abstracts of these articles were screened, and 811 studies were excluded due to irrelevant titles or abstracts, unavailability of abstracts, or non-English text. Following the full-text screening, 63 additional articles were excluded due to inappropriate results or low quality (Figure 2). As seen in Table 1, 19 studies that met all our criteria were included in our systematic review.

Alzheimer disease (AD)-related metabolites

Thirteen studies in our systematic review provided data obtained using AD model mice, rats, or *Drosophila* compared to control animals. Among these studies, [20-22] used the hippocampus or cortex as the sample source, two [22, 23] studied the cerebellum, two [24, 25] examined the blood, two [24, 26] studied urine as the sample source, and three [27-29] did not specify which part of the brain was used for analysis.

TRP

Five studies [21, 22, 25, 27, 28] measured TRP levels in 84 mice and 36 rats. Two studies measuring TRP levels in the brain tissue reported elevated TRP levels in AD model rats compared to control animals [27, 28]. Similarly, Li-Min Sun et al. [25] revealed that AD model mice have higher blood levels of TRP than controls. According to Souza et al. [21] study, mice injected with Aβ showed a significant increase in hippocampal TRP levels three days after stimulation and in the prefrontal cortex seven days after Aβ insult, compared to mice injected with vehicle. There were no significant changes to TRP concentration in the prefrontal cortex of mice 6 hours, 1 day, and 3 days following Aβ injection. Additionally, hippocampal levels of TRP in Aβ-injected mice were not significantly altered after 6 hours and 1 day of stimulation. Wu et al. [22] stated that AD brains consume more TRP in the cerebellar and hippocampal regions. They also observed increased TRP degradation in the hippocampus, cerebellum, and cortex of 3xTg AD mice compared to wild-type mice. This increase was related to increased AD mice's age [22].

L-KYN

Five studies [20-22, 24, 29] measured L-KYN levels in 76 mice, 10 rats, and *Drosophila*. According to a study by Morgese et al. [20], KYN in the cortex and hippocampus of AD model mice were significantly increased compared to controls. Furthermore, Morgese et al. [24] reported elevated KYN concentrations in the hypothalamus of AD model rats but no difference in plasma and urine KYN levels compared to control animals [24]. Souza et al. [21] reported significantly higher KYN levels in the prefrontal cortex and hippocampus of Aβ-injected mice 1, 3, and 7 days after injection compared to control animals; however, elevated KYN levels were not detected 6 hours after injection. Also, Smith et al. [29] reported that KYN levels in the brains of AD models in *Drosophila* are significantly higher than in their healthy controls. In contrast, Wu et al. [22] identified no differences in KYN concentration in AD model mice's hippocampus, cerebellum, and cortex compared to non-transgenic controls [22]. This finding is due to the rapid metabolization of KYN along QUIN pathways. This result was approved by upregulated expression of 3-hydroxyanthranilic acid oxidase, amino-carboxymuconate-semialdehyde decarboxylase, and quinolinate phosphoribosyltransferase mRNA in the cerebellum of 3xTg AD brain [22].

5-HT

Three studies [20, 24, 28] assessed 5-HT levels in 12 mice and 28 rats. Xu et al. [28] found significantly higher levels of 5-HT in the brain samples of AD model rats compared to control animals. Moreover, a study by Morgese et al. [20] reported elevated concentrations of 5-HT in the cortex of AD model mice compared to controls but no significant variance in 5-HT in the hippocampus. Also, in contrast to the abovementioned studies, Morgese et al. [24] demonstrated decreased levels of 5-HT in the brain, plasma, and urine of AD model rats compared to control animals. In their model, they observed a reduction in 5-HT levels in the hypothalamus of treated rats. Therefore, such contrasting results, as found in the behavioral paradigms used, likely result from the

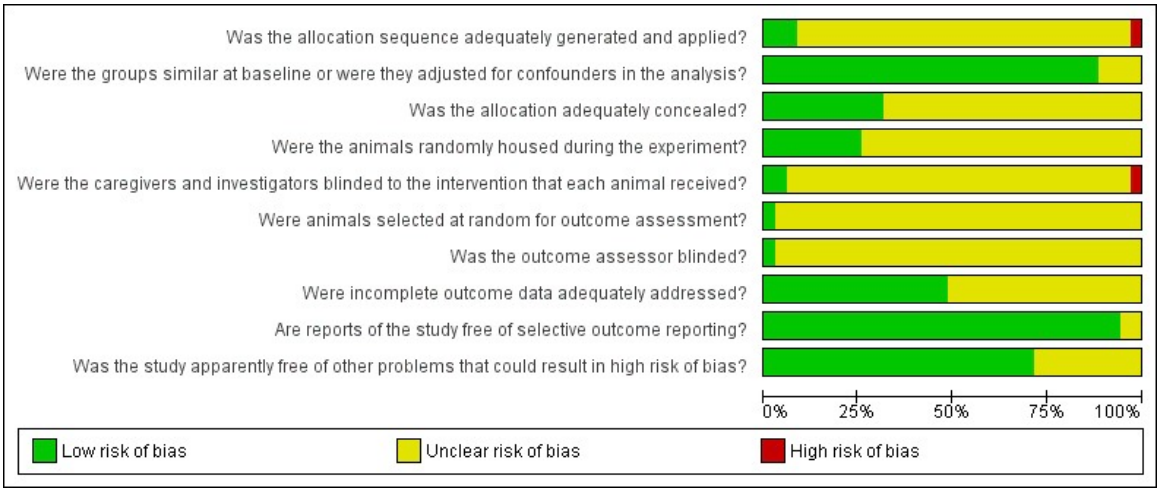

Figure 1. Quality assessment of the included studies

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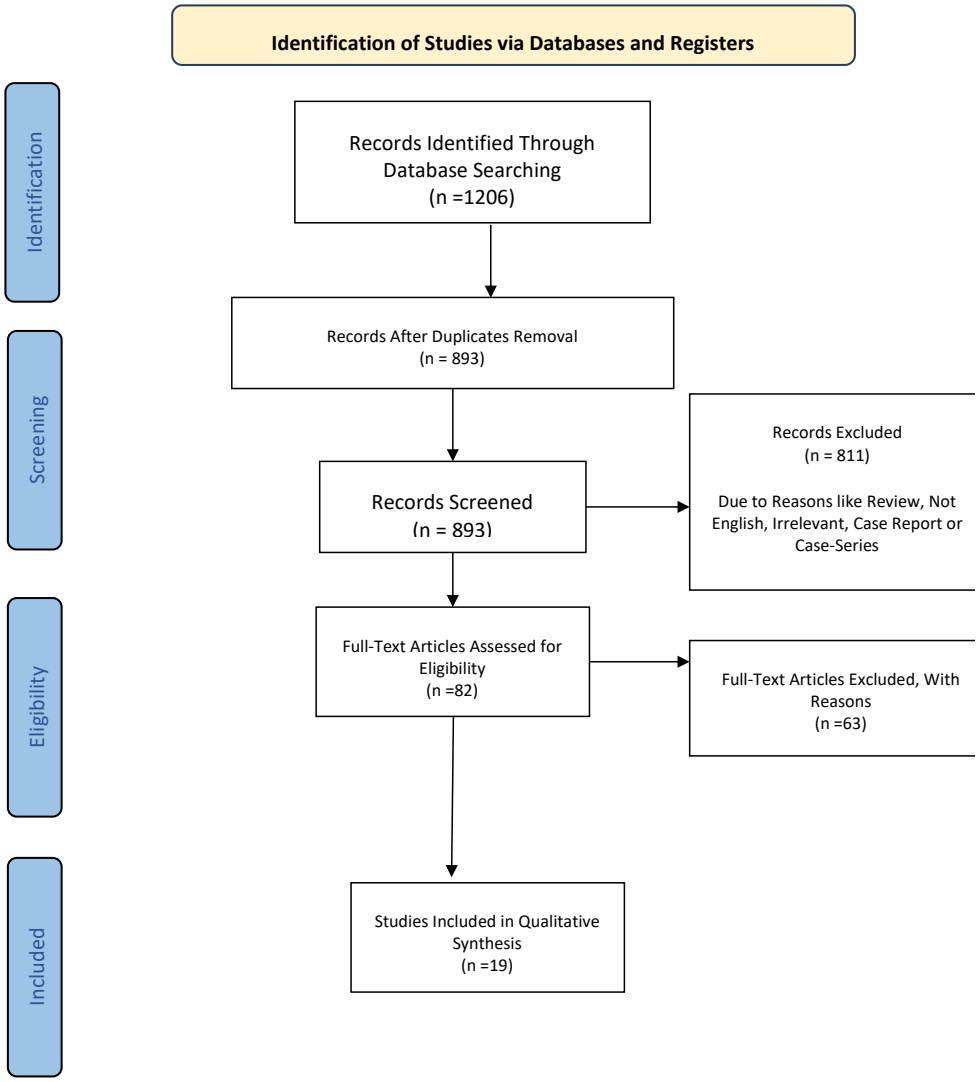

Figure 2. Flowchart of included studies in the systematic review

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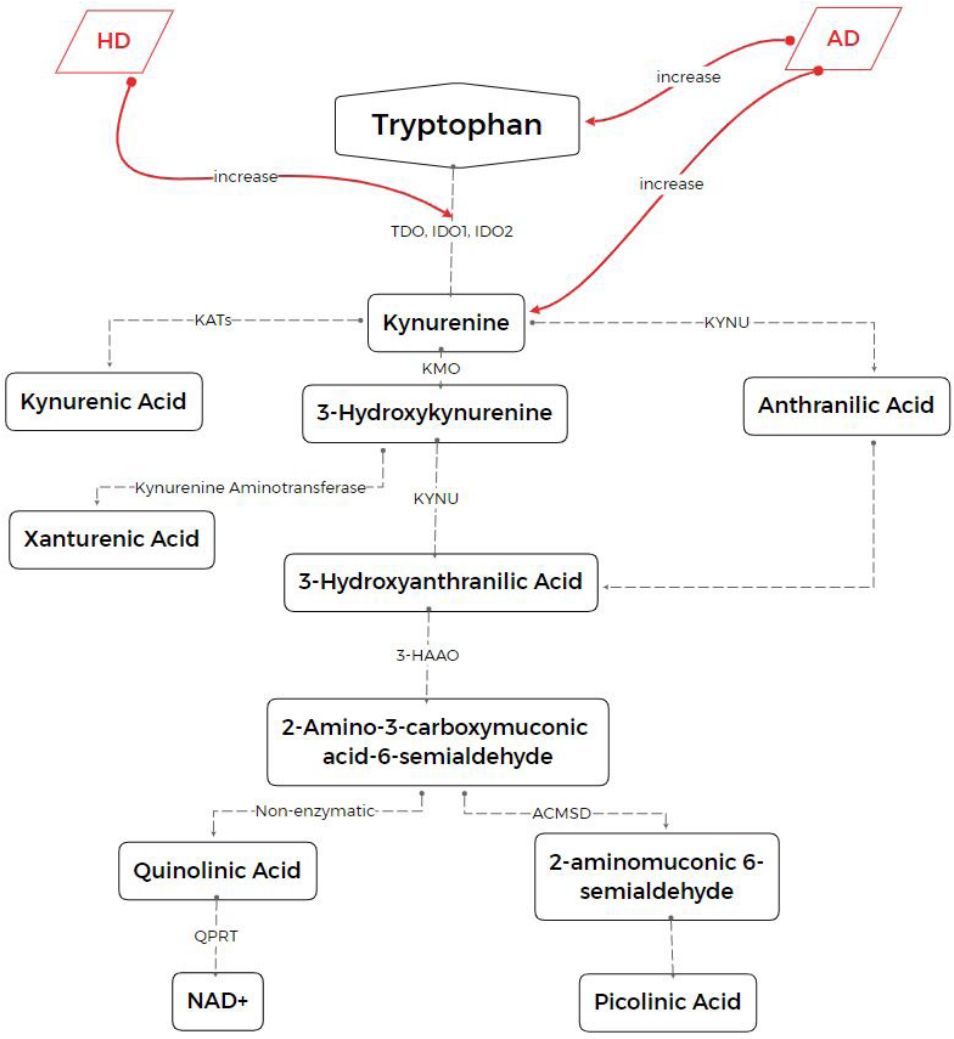

Figure 3. TRP metabolism and the KP in AD and AD

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selective activation of glutamatergic and serotonergic pathways associated with inflammatory states [24].

QUIN

This review included four studies [22, 23, 30, 21] analyzing QUIN concentrations in mice. Wu et al. [22] showed remarkably upregulated QUIN amounts in the hippocampus of AD model mice compared to the non-transgenic control group. In addition, QUIN amount was positively correlated with age in all mice. There was no difference in QUIN concentration in the cerebellum and cortex of AD model mice compared to controls. Fertan et al. [23] identified elevated cerebral levels of QUIN in 17-month-old AD model mice compared to age-matched non-transgenic controls; however, there was no significant difference between QUIN concentration in the cerebrum of 7-month-old and 17-month-old AD model mice. Sorgdrager et al. conducted a study investigating the impact of TRP 2,3-dioxygenase prevention on KYN metabolism and cognitive function in the APP23 mice model of AD [30]. Their analysis revealed that APP23 mice exhibited reduced concentrations of QUIN in their serum compared to wild-type mice, with an effect of genotype. Furthermore, the study found that aging influenced the concentrations of QUIN in both wild-type and APP23 mice serum. These findings are consistent with previous research on humans [31, 32], suggesting that QUIN levels increase during the aging process in mice [30].

KYN/TRP

This review included two studies [20, 21] that assessed the KYN/TRP ratio in 64 mice. Wu and colleagues [22] reported an increased ratio of KYN/TRP in the hippocampus, cortex, and cerebellum of AD model mice compared to non-transgenic control animals; furthermore, the KYN/TRP ratio was positively associated with the

age of AD model mice. Additionally, Souza et al. [21] identified an increased KYN/TRP ratio in mice's prefrontal cortex and hippocampus 1, 3, and 7 days after Aβ injection; this difference was not detectable 6 hours after Aβ injection [21].

IDO

Three studies [21-23] evaluated IDO levels in 82 mice. Fertan et al. [23] reported higher levels of IDO in the cerebrum of 17-month-old AD model mice compared to controls and 7-month-old AD model mice. Moreover, Souza et al. [21] revealed that IDO activity was considerably higher in mice's prefrontal cortex and hippocampus 3 and 7 days post Aβ injection compared to a sham group; however, this difference was not statistically significant 6 hours or 1 day after injection. Wu et al. [22] found no significant difference in AD mice's hippocampus, cortex, and cerebellum IDO concentrations compared to non-transgenic control animals.

TRP dioxygenase

Wu et al. measured the level of this metabolite in the cerebellum of 3xTg AD mice. Results showed that TRP dioxygenase (TDO) mRNA expression was significantly elevated in 6-8-month- and 10-12-month-old AD mice compared to age-matched controls ($P<0.01$ and $P<0.001$, respectively) [22]. In another study, the effect of oral administration of the TDO inhibitor 680C91 on recognition memory in a mice model of AD was positive. The study showed that the administration of this inhibitor improved recognition memory in AD mice [33]. In the study of Sorgdrager et al., the results indicate that extended use of the TDO inhibitor 680C91 has minimal impact on the KYN metabolite profiles in the blood of both APP23 and wild-type mice. Furthermore, it does not alter the levels of KYN metabolites in the cortex, hippocampus, and cerebellum [30]. Woodling et al. discovered a trend toward an increase in TDO2 protein levels in the hippocampus of APPPS1 mice at the protein level [33]. However, this trend is not reflected at the RNA level, indicating that changes in translation, post-translational modification, and degradation of TDO2 protein may contribute to these differences. They also observed that ibuprofen significantly reduced hippocampal KYN levels, the main product of TDO2 enzymatic activity. Interestingly, this effect is more pronounced in wild-type mice than APP-PS1 mice, suggesting that there may be alterations in the downstream metabolism of KYN in APP-PS1 mice as well [33].

KYNA

Sorgdrager et al. conducted an experimental study to assess the impact of aging on KP activity in mice, specifically on neurodegeneration [30]. They examined KYNs in APP23 and wild-type mice serum at 3, 6, and 12 months of age. The analyses indicated that age and genotype did not interact to impact serum concentrations of KYN metabolites. In terms of genotype, the analyses revealed lower concentrations of KA. The findings suggest a correlation between aging and changes in KA in the cortex [30]. Zwilling et al. assessed the impact of systemic administration of JM6, a KMO inhibitor, on the brain's KP [34]. They conducted in vivo microdialysis in the striatum of awake rats. They aimed to measure extracellular KYNA as a pharmacodynamic indicator of KMO inhibition in the periphery. Following a single oral dose of JM6 (100 mg/kg), they observed increased KYNA levels in both the brain and serum [34]. Chronic therapy of APPtg mice with JM6 (75 mg/kg/d PO for 120 days) increased KYNA levels in the brain and plasma. This finding is significant because APPtg mice initially had lower brain KYNA levels than wildtype littermate controls. However, it is worth noting that the levels of KMO activity, 3-HK, and QUIN in the brains of APPtg mice treated with JM6, as well as QUIN levels in the plasma, did not show any significant differences compared to the control mice [34].

3-HK, xanthurenic acid, and 3-hydroxyanthanilic acid

Sorgdrager et al. analysis of serum levels of 3-HK and xanthurenic acid (XA) in APP23 mice compared to wild mice revealed reduced concentrations of 3-HK and XA in the serum of APP23 mice [30]. They also revealed a correlation between aging and changes in 3-Hk cortex level [30]. Aging led to alterations in the concentrations of XA and 3-hydroxyanthanilic acid (3-HAA) in the serum of both wild-type and APP23 mice [30].

AD metabolites

This systematic review included six studies [34-39] using HD animal models. All studies [35-38] used the striatum as a sample source. Additionally, three studies [35, 36, 38] included the cortex, two [37, 38] analyzed the cerebellum and plasma, and one [38] used the hippocampus and brain stem as the sample source.

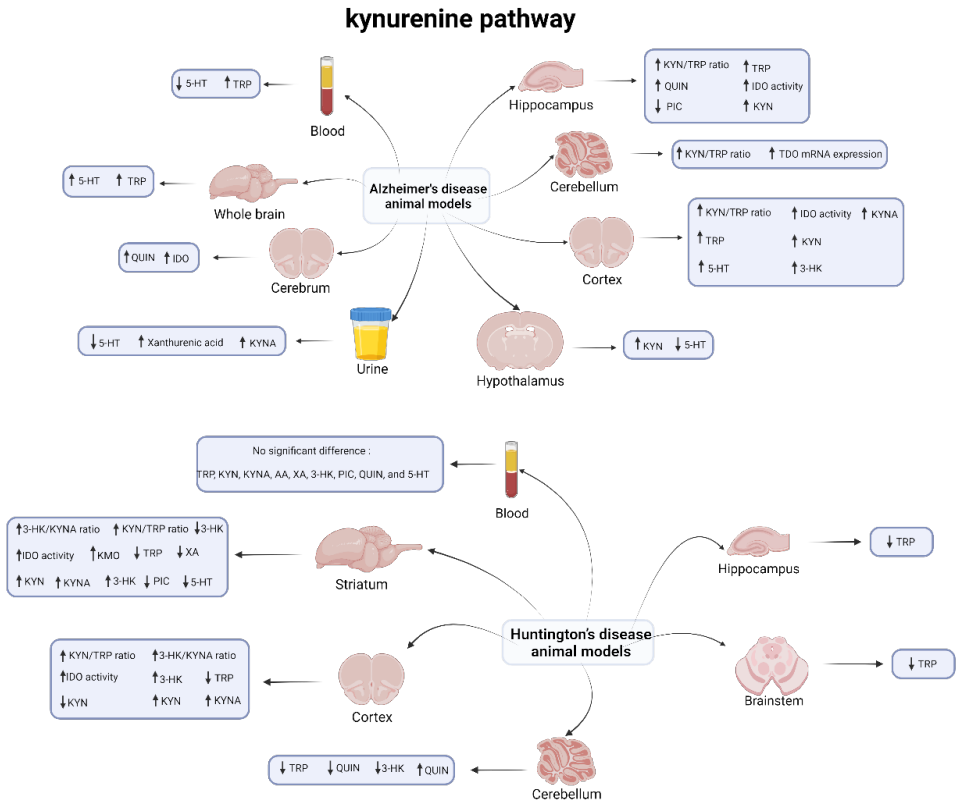

Figure 4. Alterations of KP in Animal models of AD and AD

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TRP

Three studies [35, 37, 38] assessed TRP levels in 90 mice. Veres et al. [38] demonstrated decreased TRP levels in the striatum, cortex, hippocampus, cerebellum, and brainstem of HD model mice compared to control animals; however, serum TRP levels were comparable in HD model mice and control animals. Mazarei et al. [37] reported decreased levels of TRP in the striatum of 3-month-old HD model mice in comparison to age-matched non-transgenic control mice; this difference was not detected in the cerebellum of 3-month-old HD model mice and their control. Additionally, compared to control mice, no significant differences were found in the striatum, cerebellum, or plasma TRP levels of 12-month-old HD model mice. Interestingly, Donley et al. [35] did not report a significant difference in TRP concentration in the cortex or striatum of HD model mice compared to control animals.

KYN

Three studies [35, 37, 38] measured KYN levels in 90 mice. Donley et al. [35] revealed significantly elevated KYN concentrations in the cortex and striatum of HD model mice compared to control animals. Similarly, Veres et al. [38] reported increased KYN concentrations in the cortex of HD model mice; however, this difference in KYN concentration was not present in the striatum, hippocampus, cerebellum, brainstem, or serum of HD model mice when compared to control. Mazarei et al. [37] reported higher levels of KYN in the striatum of 12-month-old HD model mice compared to control animals; however, in the cerebellum and plasma, both experimental groups showed similar KYN concentrations. Similarly, there was no statistically significant difference in the striatal or cerebellar KYN levels of 3-month-old HD model mice.

KYNA

Four studies [35-38] analyzed KYNA levels in 104 mice. Guidetti et al. [36] revealed significantly elevated KYNA levels in the cortex and striatum of HD model mice. However, Veres et al. [38] reported comparable KYNA levels in the cortex and serum of HD model mice and control mice. Of note, KYNA concentrations in these animals' striatum, hippocampus, cerebellum, and brainstem were below the detection limit. Similarly, Donley et al. [35] revealed no significant difference between KYNA levels in the cortex and striatum of HD model mice compared to non-transgenic controls. Maz-

Table 1. Summary of the main findings from studies included in the systematic review

Study (Reference)	Disease	Experimental Group		Control Group		Age (m)	Sample Source	Metabolites	Method
		Type	No.	Type	No.				
Wu et al. 2013 [22]	AD	3xTg AD mice	4	Wild-type mice	4	2-4 6-8 10-12 2-4 6-8 10-12 2-4 6-8 10-12	Hippocampus Cerebellum Cortex	TRP, KYN, QUIN, PIC, IDO1, TDO, KYN/TRP	HPLC or GC-MS
Souza et al. 2016 [21]	AD	Aβ-injected mice	8	Sham mice	8 8	3	Prefrontal Cortex Hippocampus	TRP, KYN, KYN/TRP	HPLC
Sun et al. 2018 [25]	AD	APP/PS1 mice	10	Wild-type mice	10	5	Blood	TRP	HPLC-UV
Xu et al. 2018 [28]	AD	AD model rats induced by D-gal and Aβ25–35	8	Saline injected rats	8	-	Brain sample	TRP, 5HIAA, 5-HT	LC-MS/MS
Sun et al. 2018 [27]	AD	AD model rats induced by D-gal and Aβ25–35	10	Saline injected rats	10	-	Brain sample	TRP	HPLC-MS/MS
Fertan et al. 2019 [23]	AD	3xTg-AD mice	5 4	Wild-type mice	5 4	7 17	Cerebrum	IDO, QUIN	-
He et al. 2020 [26]	AD	Aβ-injected rats	12	Saline injected rats	12	-	Urine sample	KYNA, xanthurenic acid	UHPLCQ-TOF-MS
Morgese et al. 2021 [20]	AD	Mice received Aβ 1-42	6	Mice received only vehicle	6	2-3	Cortex Hippocampus	KYN, 5-HT	HPLC
Morgese et al. 2022 [24]	AD	Aβ1–42-injected rats	5	Vehicle injected rats	5	1.75	Hypothalamus Plasma Urine	5-HT, KYN	HPLC
Smith et al. 2022 [29]	AD	AD model of *Drosophila* with co-expression of hAβPP and hBACE	-	Bloomington stock w1118	-	14-day old	Head	KYN, 3-HK	HPLC
Sorgdrager et al. 2020 [30]	AD	Male heterozygous APP23	-	Wild-type mice	-	3, 6, and 12 old months	Blood, bilateral hippocampi, cortex, and cerebellum	KYNA, QUIN, 3-HK, XA, 3-HAA. and TDO	HPLC/MS-MS

Study (Reference)	Disease	Experimental Group		Control Group		Age (m)	Sample Source	Metabolites	Method
		Type	No.	Type	No.				
Woodling et al. 2016 [33]	AD	APP-PS1 male mice	8	Wild-type	8	3 to 6 months	Hippocampus,	TDO	HPLC, RT-PCR
Zwilling et al. 2011 [34]	AD	APPtg mice R6/2 mice	3	Age-matched wild-type	5-13	7 months	Striatum, blood,	KYNA, QUIN, 3-HK	HPLC, GC/MS
Guidetti et al. 2000 [36]	HD	HD 89 mice	5	Wild-type mice	9	12-15	Cortex and Striatum	KYNA, 3-HK	HPLC
Mazarei et al. 2013 [37]	HD	YAC128 mice	12 6	Wild-type mice	12 10	3 12	Striatum Cerebellum Striatum Cerebellum Plasma sample Serum sample	TRP, KYN, KYNA, QUIN, PIC, AA, XA, 3-HK, 5-HT, KYN/TRP, IDO1	LC/MS/MS
Veres et al. 2015 [38]	HD	3-NP-injected mice	16	Vehicle-injected mice	14	5	Striatum Cortex Hippocampus Cerebellum Brainstem	TRP, KYN, KYNA, 3-HK	HPLC
Donley et al. 2021 [35]	HD	N171-82Q HD mice	10	Wild-type mice	10	3.5	Cortex Striatum	IDO, KMO, TRP, KYN, KYNA, 3-HK, KYN/TRP, 3-HK/KYNA	HPLC-MS/MS
Sathyasaikumar et al. 2010 [39]	HD	R6/2 female mice	3-5	Age-matched wild-type	3-5	2 weeks to 3 months	Frontal cortex and cerebellum	3-HK	HPLC
Giorgini el al. 2008 [40]	HD	R6/2 mice	3	Wildtype mice	3	2	Cortex	3-HK	HPLC or GC-MS

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arei et al. [37] also reported similar KYNA concentrations in the striatum and cerebellum of 3-month-old HD model mice and in the striatum, cerebellum, and plasma of 12-month-old HD model mice compared to controls.

3-HK

This review included six studies [35-40] measuring 3-HK concentrations in 118 mice. Donley et al. [35] and Guidetti et al. [36] demonstrated remarkably elevated 3-HK levels in the striatum and cortex of HD model mice compared to control animals. Similarly, Mazarei et al. [37] reported higher concentrations of 3-HK in HD model mice compared to non-transgenic animals; however, there was no remarkable variance in 3-HK levels in the striatum and cerebellum of 3-month-old HD model mice or the cerebellum and plasma of 12-month-old HD model mice compared with age-matched controls. Veres et al. [38] revealed significantly increased cerebellar levels of 3-HK in the HD model mice compared with controls. 3-HK concentration in the striatum, cortex, hippocampus, brain stem, and serum were below the detection limit. Sathyasaikumar et al. investigated cerebral KP metabolism in the brains of HD mice [39]. Employing

in vivo and ex vivo methods in R6/2 mice, a commonly used transgenic mouse model of HD, they examined KP flux dynamics in the striatum. They assessed the activities of key KP enzymes in three brain regions. Their findings indicate the raised generation of 3-HK in the mutant animals and identify enzymatic abnormalities that likely contribute to the accumulation of this toxic metabolite in the disease. Giorgini et al. [40] reported that the levels of 3-HK were 52% higher in the microglia of HD models of mice than in wild-type mice ($P<0.01$).

Discussion

In this systematic review, 19 research articles were reviewed to examine how the KP alters serum, urine, and brain levels of significant metabolites and enzymes related to the KP in AD and HD models. Some markers, including TRP, KYN, KYNA, QUIN, 3-HK, 5-HT, KYNA, and picolinic acid (PIC) levels, and the expression of IDO mRNA and KAT activity were examined. As described before, these metabolites' levels change significantly in these animal models according to the time of disease onset and the age of the experimental groups. It is possible for a single metabolite, such as KYN and 3-HK, to increase or decrease in the same model based on various factors, including the time and location of sampling.

The KP, illustrated in Figure 3, is one of the main metabolic pathways of tryptophan. In this pathway, L-TRP is converted to nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$), two essential co-enzymes for cellular energy production and metabolism [41]. The metabolites of the KP serve modulatory roles in various neurobiological pathways and possess diverse, sometimes opposing effects. Accumulating some of these metabolites can trigger oxidative cell damage and inflammation and disrupt the appropriate functioning and homeostasis of numerous organs and neurological systems [36]. In the first step of this pathway, TRP is catabolized to N-formylkynurenine by the action of two enzymes: TRP 2,3-dioxygenase (TDO) and two 2,3-indoleamine dioxygenase isoforms, IDO-1 and IDO-2. N-formylkynurenine is then metabolized into KYN [12]. KYN is a central metabolite of the KP, which can be further metabolized into one of three metabolites, including 3-hydroxyl-L-kynurenine (3-HK), KYNA, and anthranilic acid (AA) [12]. KYN is a neuroprotective agent that reducing oxidative stress by scavenging hydrogen peroxide and superoxide ions; however, some of these effects may be attributed to its metabolite, KYNA [4]. Conversion of KYN into 3-HK occurs through the action of KYN 3-monooxygenase (KMO) [42]. 3-HKYN can then be transformed into XA by KAT or to 3-hydroxy anthranilic acid (3-HA) through kynureninase [43, 44]. Even low levels of 3-HKYN and 3-HA can induce oxidative stress, leading to neurotoxic damage [45, 46]. 3-HA is metabolized to 2-amino-3-carboxymuconic acid-6-semialdehyde (ACMS) by the enzyme 3-hydroxyanthranilic acid 3,4-dioxygenase (3-HAO). ACMS can then be converted to PIC through a non-enzymatic cyclization or QUIN through a non-enzymatic transformation. Quinolinate phosphoribosyltransferase (QPRT) transforms QUIN into NAD^+ [12] (Figures 3 and 4). Oxidative stress through the activity of 3-HK and 3-HA causes neuronal tissue damage, amyloid-β accumulation, and up-regulation of KP, consequently leading to neurodegeneration and neuroinflammation in AD [47].

QUIN is a neurotoxic metabolite that directly activates neurons' N-methyl-D-aspartate (NMDA) receptors, which causes inhibition of glutamate reuptake, leading to increased Ca^{2+} influx into the target neurons and causing neuron damage and death, a process called excitotoxicity [48]. Moreover, microglia activation through their NMDA receptors induces neuronal cell death [49]. QUIN promotes neurotoxic effects through several pathways, including excessive generation of ROS, increased phosphorylation of tau, disruption of blood-brain barriers, destabilization of cellular cytoskeleton, and impaired autophagy [50, 51, 52]. During normal conditions in the brain, most TRP is catabolized into 5-hydroxytryptamine rather than formyl KYN, resulting in a lower concentration of neurotoxic metabolite, QUIN. However, during systemic inflammation or neuroinflammation, infiltration of inflammatory cells, including macrophages, dendritic cells, and microglia, produces higher amounts of QUIN and makes the brain environment susceptible to inflammatory damage [53].

The amyloid beta peptide (Aβ1-42) triggers the expression of IDO1, subsequently rising in excessive production of QUIN by human primary macrophages and microglia [54]. It is well known that increasing the production of KP neurotoxic species compared to neuroprotective metabolites of this pathway contributes to the pathogenesis of AD [13, 55]. According to the included studies, KYN and TRP levels are higher in the central nervous system of AD model animals compared to corresponding controls. However, it is identified comparable levels of KYN and TRP in AD models and controls, possibly due to the rapid metabolism of KYN and TRP in AD triple transgenic mice [22]. Increased production of IDO has been shown in the neocortex and hippocampus of AD patients [47] and is correlated with a load

of Aβ plaque [56]. Moreover, chronic stress and neuroinflammation enhance IDO and TDO, leading to the shunting of TRP to KP and the generation of neurotoxic metabolites of KP [57]. Genetic and pharmacological inhibition of KMO in a fruit fly model of HD increased KYNA/3-HK levels and inhibited neurodegeneration. Similarly, genetic inhibition of TDO shifted the production of KP towards KYNA synthesis. Therefore, it could be concluded that through inhibition of KMO and TDO activity, neuroprotection against neurodegeneration and neuroinflammation could be achieved [58].

The metabolites of the KP have diverse effects on biological processes. AA exhibits antioxidant activity and can downregulate ROS formation, while XA mainly acts as a neurotoxic metabolite similar to its precursor, 3-HKYN [59, 60]. Furthermore, PIC is a non-selective metal ion chelating metabolite and neuroprotective agent; its potency against QUIN-associated neurotoxicity is related to its capacity to chelate zinc. PIC's protective efficacy against QUIN's neurotoxic activity is lower than KYNA but higher than AA [61]. KYN is transformed into KYNA through an irreversible reaction catalyzed by KAT [62]. KYNA is an antioxidant because it can scavenge free radicals, including hydroxyl and superoxide anions [13]. At nanomolar concentrations, KYNA exhibits neuromodulatory and neuroactive effects; however, at micromolar and above physiological concentration range, KYNA displays an inhibitory effect on neuronal systems [63, 64]. At physiological concentrations (nanomolar concentrations), this metabolite acts as a non-competitive antagonist of α7-nicotinic acetylcholine receptors, causing a reduction in acetylcholine, glutamate, and dopamine signaling [65]. Above physiological levels (micromolar levels), KYNA acts as a non-selective antagonist of NMDA receptors [66]. Solvag et al. identified reduced plasma levels of KYNA in AD patients [67]. A similar trend of decreased plasma KYNA was revealed in patients with PD and HD [68]. KYNA modulates immune responses through its agonistic effects on the aryl hydrocarbon receptor (AhR). AhR is an essential transcription factor in the termination of cytokine release from immune cells, including macrophages. Moreover, KYNA acts as an agonist at an orphan G-protein-coupled receptor (GRP35), regulating the production of cAMP and inhibiting N-type Ca^{2+} channels of astrocytes, suppressing inflammatory responses [69, 70]. These observations suggest that reduced levels of KYNA may promote inflammation in AD, PD, and HD by decreasing the production of anti-inflammatory cytokines, leading to tissue damage and increased cell proliferation [12].

The mechanism by which the KP is involved in the pathogenesis of HD has not been fully elucidated; however, immune activation occurs during HD progression in the brain and contributes to abundant production of inflammatory cytokines, including tumor necrosis factor α (TNF-α) and various interleukins which are higher in post-mortem brain tissue and blood of HD patients compared to control [71]. Activation of neuroinflammation and microglia during the HD process leads to enhanced IDO activity and downstream activation of KP metabolites. Several studies have supported the involvement of KP in HD progression. Levels of QUIN and 3-HK increased in the cortex and neostriatum of HD patients at the early stages of the disease [72]. Consistently, in the mouse models of HD, brain levels of QUIN and 3-HK are upregulated [73]. The included studies show elevated neurotoxic KP metabolites are observed in HD model animals, similar to AD models. However, further investigation into this metabolic pathway is warranted due to the inconsistency of KP-related data reported by these studies.

As our understanding grows, it becomes clear that KP metabolites directly and indirectly impact the development of several human diseases. This finding surged the interest in using these roles as a basis for medication development. Pharmacological interventions have primarily focused on inhibiting important enzymes in KP, such as IDO, TDO, and KMO. Specifically, the focus on inhibiting IDO1, which plays a role in immune suppression and tumor growth, has gained attention as a promising strategy in cancer treatment development [74, 75]. Comprehensive reviews in recent literature [76, 77] have discussed this subject's preclinical and clinical evidence extensively. Despite the negative results of recent phase III trials, there are concerns about the role of IDO1 in neurodegenerative disorders. However, experts in the field believe that a more comprehensive understanding of the regulation and downstream mediators of TRP metabolism is necessary to fully exploit the KP's potential in treating neurodevelopmental disorders. The scarcity of pertinent studies investigating the KP can be attributed to the recent elucidation of its functions in bone and muscle metabolism.

Conclusion

In conclusion, changes in the levels of KP metabolites and enzymes are observed in several in vivo studies on mice or rat models of AD and HD. Increased levels of TRP and KYN are seen in specific brain regions of AD model animals. Also, inconsistent changes in the neurotransmitter 5-HT, increased QUIN concentrations in

the hippocampus, and elevated KYN/TRP ratios across various brain regions are observed. The activity of enzymes involved in TRP metabolism, such as IDO and TDO, displays multiple patterns. However, KYNA levels do not consistently change, suggesting a need for further investigation. In AD, alterations in tryptophan, KYN, KYNA, and 3-HK levels are observed in different brain regions of HD model mice, with a consistent elevation of 3-HK in the striatum and cortex. Thus, assessing the alterations in KP metabolites or enzymes can potentially be promising in diagnosing AD and HD, especially in earlier stages. Also, KP changes in AD and HD may suggest therapeutic approaches affecting this pathway in these two diseases. Further research is needed to comprehensively compare KP metabolites and enzymes between AD or HD models and controls and assess their roles in diagnosing and treating these diseases.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Critical Care Quality Improvement Research Center, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Code: IR.SBMU.RETECH.REC.1402.763).

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Authors contributions

Investigation and writing: All authors; Supervision, conceptualization, and methodology: Mohammaderza Hajiesmaeili and Navid Nooraei. Farzaneh Ahmadi and Saleh Behzadi contributed equally to the paper.

Conflict of interest

The authors declared no conflicts of interest.

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