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Tryptophan metabolites modify brain A β peptide degradation: A role in Alzheimer's disease?

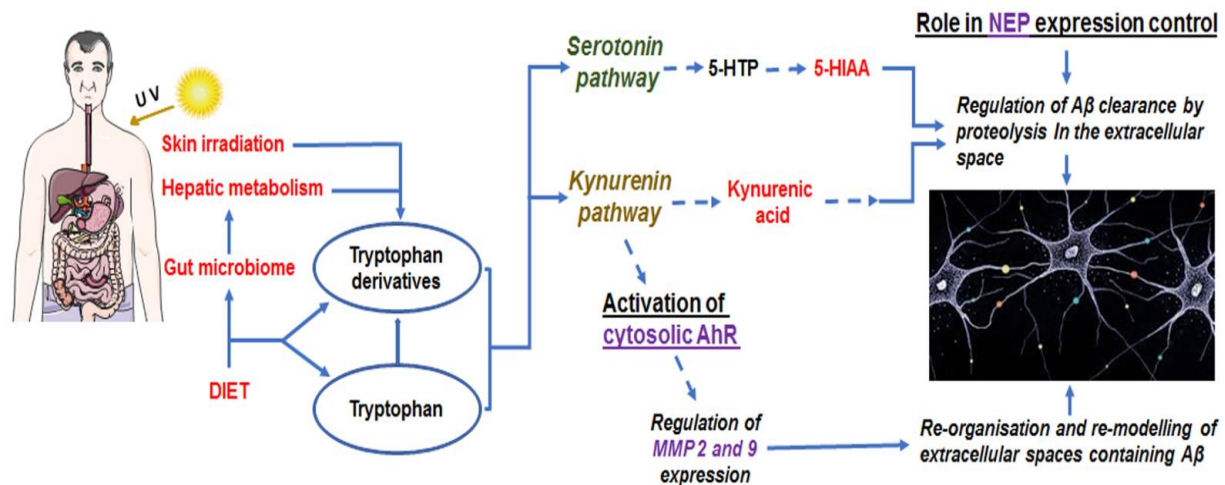
Michel Maitre*§ (ORCID 0000-0003-1478-4806), Christian Klein, Christine Patte-Mensah, and Ayikoe-Guy Mensah-Nyagan*§ (ORCID 0000-0003-4454-511X)

Biopathologie de la Myéline, Neuroprotection et Stratégies Thérapeutiques, INSERM U1119, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, Bâtiment 3 de la Faculté de Médecine, Strasbourg, France.

§ Correspondence to Prof. M. Maitre (maitre@unistra.fr) or Prof. A.G. Mensah-Nyagan (gmensah@unistra.fr).

Abbreviations: AD, Alzheimer's disease; NEP, neprilysin; 5-HIAA, 5-hydroxyindole-acetic acid; KYNA, kynurenic acid; IDO, indolamine 2,3-dioxygenase; KMO, kynurenine 3-monooxygenase; APP, amyloid precursor protein; AhR, aryl hydrocarbon receptor; MMP, matrix metalloproteinases; TDO, tryptophan dioxygenase; KATs, kynurenines aminotransferases; ROS, reactive oxygen species; TPH, tryptophan hydroxylase; 5-HT, 5-hydroxytryptamine (serotonin); 5-HTP, 5-hydroxytryptophan; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; QUIN, quinolinic acid.

Graphical Abstract



Tryptophan and tryptophan derivatives in the body originate from various sources including diet, gut microbiome, hepatic metabolism and photo-oxidation producing 6-formylindolo [3,2-b] carbazole; FICZ. These substances are present in brain, especially in neuro-inflammatory and neurodegenerative processes (Alzheimer's disease) with disrupted blood brain barrier. Serotonin and kynurenine pathways compete to produce kynurenic acid and 5-HIAA. These two compounds have been shown to induce the brain neutral endopeptidase neprilysin that ameliorate amyloid peptides clearance. 5-HIAA promotes cognitive process in a mouse model of Alzheimer's. Numerous tryptophan derivatives, including FICZ and possibly serotonin, stimulate AhR mediated transcription of some matrix metalloproteinases (especially MMP 2 and 9) which participate in the extracellular rebuilt and A β clearance. These results shed some light on the role of tryptophan and derivatives in the pathophysiology and possible preventive approach of amyloid peptides accumulation in brain.

Highlights

Brain A β peptide degradation and clearance are controlled by neprilysin

Tryptophan metabolites modulate several metalloproteinases including neprilysin

Tryptophan metabolites 5-HIAA or KYNA induce brain or neuronal neprilysin expression

5-HIAA reduces brain A β peptides and improves memory deficits in a mouse model of AD

KYNA induces neprilysin to prevent or counteract A β peptide-induced neurotoxicity

Abstract

Among several processes, a decrease in amyloid-beta ($A\beta$) peptide elimination is thought to be one of the major pathophysiological factors in Alzheimer's disease (AD). Neprilysin (NEP) is a key metalloproteinase controlling the degradation and clearance of $A\beta$ peptides in the brain. NEP is induced by several pharmacological substances, amyloid deposits and somatostatin, but the physiological regulation of its expression remains unclear. This situation hampers the exploitation of NEP regulatory factors/mechanisms to develop effective strategies against $A\beta$ peptide accumulation-induced brain toxicity. Based on recent data aimed at elucidating this major question, the present paper addresses and critically discusses the role of 5-hydroxyindoleacetic acid (5-HIAA) and kynurenic acid (KYNA) in the regulation of NEP activity/expression in the brain. Both 5-HIAA and KYNA are endogenous metabolites of tryptophan, an essential amino-acid obtained through diet and gut microbiome. By interacting with the aryl hydrocarbon receptor, various tryptophan metabolites modulate several metalloproteinases regulating brain $A\beta$ peptide levels under normal and pathological conditions such as AD. In particular, interesting data reviewed here show that 5-HIAA and KYNA stimulate NEP activity/expression to prevent $A\beta$ peptide-induced neurotoxicity. These data open promising perspectives for the development of tryptophan metabolite-based therapies against AD.

Keywords: Tryptophan; tryptophan derivatives; Alzheimer's disease; Matrix metalloproteinases; Neprilysin; amyloid peptides.

Alzheimer's disease and tryptophan metabolism

Sporadic AD is the most common age-related neurodegenerative disease in industrialized countries (Reitz *et al.*, 2011). AD, which affects about 40 % of people over 80, seems to be a human disorder because non-human primates do not develop this pathology despite the fact that they also exhibit genetic, molecular and cellular brain changes with age (Prpar Mihevc and Majdic, 2019). The major histopathological hallmarks of AD are the progressive accumulation of A β oligomers and plaques in the brain and the abnormal deposits of hyperphosphorylated Tau protein (neurofibrillary tangles) inside neurons, leading to neuronal degeneration in multiple brain areas. A β peptides composed of 38-43 amino-acids are derived from the proteolytic processing of the amyloid precursor protein (APP) (Kovacs, 2016; Robinson *et al.*, 2018). The classical clinical onset of AD consists of cognitive dysfunctions with a progressive deficit in short- and long-term memories. The amyloid hypothesis states that an excessive production of A β peptides resulting from the cleavage of APP by β and γ secretases is the cause of multiple pathological changes (calcium homeostasis, inflammation, astrogliosis, DNA mutations including mitochondrial DNA, alterations of cell cycle and energy metabolism), hyperphosphorylation of Tau and axoplasmic traffic disturbances leading to synaptic and neuronal loss, brain atrophy with worsening dementia (De-Paula *et al.*, 2012). Behavioral and psychological symptoms appear early in the progression of the disease and usually consist of mood, emotional and appetite disturbances, together with modifications of sleep and circadian rhythms, depression, confusion, anxiety and agitation. All components of this symptomology are usually related to the alterations of serotonergic pathways and nuclei since the brainstem, particularly the serotonergic Raphe nuclei exhibit early pathological changes in the development of AD (Rodriguez *et al.*, 2012; Rub *et al.*, 2000; Simic *et al.*, 2017). Pharmacological targeting of the serotonergic system is most often used to improve the progression and clinical expression of the disease. Some specific treatments include 5-HT₄ receptors agonists and 5-HT₆ receptors antagonists. The beneficial effects increase the global quality of life as a result of an improvement in depressive symptoms, learning, memory and cognition. Also, inhibition of the serotonin transporter has been reported to influence A β peptide accumulation (Claeyssen *et al.*, 2015).

The kynurenine pathway has also been implicated in the early stages of AD pathophysiology. Indeed, two metabolites of this pathway, namely the neuroprotective kynurenic acid (KYNA) and the neurotoxic quinolinic acid (QUIN), contribute to pathophysiological changes occurring in AD through their modulatory effects of neuronal survival. The enzymatic activities of indoleamine-2,3 dioxygenase (IDO), tryptophan-2,3 dioxygenase (TDO), kynurenine-3-monooxygenase (KMO) and kynurenine aminotransferases (KATs) have all been described as modulators in the alterations of kynurenine metabolism leading to neuronal toxicities. Thus, the ratio between neuroprotective and neurotoxic compounds or the balance between kynurenine and serotonin pathways seems to be determinant in the development of neurodegenerative processes (Lovelace *et al.*, 2017). In support of this idea, it has been shown that in chronic neuroinflammatory conditions, pro-inflammatory cytokines induced the expression of IDO and TDO which decrease the availability of tryptophan for serotonin/5-HIAA production by driving the system towards the kynurenine pathway (Li *et al.*, 2017). Additional evidence for the involvement of tryptophan catabolites in neurodegeneration has also been provided by studies performed with the cerebrospinal fluid of AD patients (Kaddurah-Daouk *et al.*, 2013; Maes and Anderson, 2016).

The pathophysiological mechanisms of AD suggest that A β synthesis and degradation are linked with the impairment of extracellular protein clearance that may play an important role. In many cases, protein-related disorders in aged or AD patients are not limited to the brain but represent the result of several molecular and functional abnormalities that also affect peripheral organs. The gastro-intestinal tract and its enormous population of microorganisms that is influenced by diet participate in the production of several neurotransmitters and precursors that are delivered by a leaky intestine and penetrate the brain through a disrupted blood-brain barrier (Zhuang *et al.*, 2018). A long process of neuroinflammation, vascular alterations and decreased blood flow in the brain precede neuronal and synaptic death in a long period of preclinical incubation followed by a progressive neurodegenerative phenomenon. A β accumulation and toxicity are revealed by this cellular phase in parallel with neurological symptoms (De Strooper and Karran, 2016). Several defective clearance mechanisms of A β could include the ubiquitin-proteasome system, autophagy/lysosome pathways and microglial phagocytosis. A role for A β transport from the periphery to the brain by macrophages has also been implicated in intravascular and extracellular A β accumulation which disseminates the proteinopathy (Cintron *et al.*, 2015). The removal of

accumulated A β also critically depends on A β proteolysis that involves several extracellular proteases, including insulin-degrading enzyme, matrix metalloproteinases, endothelin converting enzyme, angiotensin converting enzyme and plasmin (Xin *et al.*, 2018). But among these enzymes, neprilysin (NEP) has been identified as the most efficient. Indeed, a deficiency or decrease in NEP activity in the brain induces an important reduction of A β clearance that leads to the modification of A β turnover and cerebral accumulation in late-onset AD (Baranello *et al.*, 2015).

Neprilysin and A β clearance

NEP is considered one of the most active extracellular proteases that degrade amyloid oligomers and plaques in the CNS. It is a membrane-bound zinc neutral endopeptidase (24.11, or enkephalinase, CD10 antigen) of 750 amino acid residues encoded by a four splice variants gene. NEP is also present in the kidney and lung and participates in the regulation of blood pressure. NEP gene expression is controlled at least by two promoters and varies between different tissues. In the brain, NEP is expressed by neurons (mainly in axons and synapses) but also by activated astrocytes and microglia (Iwata *et al.*, 2004). NEP gene inactivation (-/-) in mice or NEP inhibition by phosphoramidon or thiorphan causes an accumulation of brain A β peptides, suggesting that a decrease in NEP activity may promote A β deposition (Shirotani *et al.*, 2001). In humans, NEP levels decrease with age in multiple brain regions (e.g. cortex, hippocampus) and NEP is over-expressed in astrocytes surrounding amyloid plaques (Nalivaeva *et al.*, 2012b). Several studies have reported significant decreases in NEP protein and mRNA in aged animals, including *Drosophila*, mice, rats and human (Grimm *et al.*, 2013).

NEP cleaves a wide spectrum of peptides involved in neurotransmission/neuroregulation (e.g. enkephalins or substance P, bradykinin, Neuropeptide Y, tachykinins, somatostatin) but it is also very active in regulating the amount of A β peptides by cleaving them at different sites and thus facilitating their elimination from the brain. These effects prevent the accumulation of toxic peptides and their deleterious consequences for neurons and synapses survival. A β 42 deposits and neuronal loss are largely suppressed in transgenic *Drosophila* expressing human NEP and A β 42 (Iijima-Ando *et al.*, 2008). Therefore, the mechanism(s) that drive the regulation of NEP

expression in brain are of special interest. Indeed, genetic experiments have shown that the early induction of NEP over-expression in transgenic mice may improve cognitive performance (El-Amouri *et al.*, 2008). It has also been reported that NEP activity and gene expression are regulated by various factors including the level of AICD (C-terminal APP intracellular domain) and pharmacological treatments with polyphenols, plant extracts, somatostatin receptor ligands, Gleevec or valproate (Nalivaeva *et al.*, 2012a). Decreased levels of somatostatin, estrogens and vitamin D were correlated to a down-regulation of brain NEP, leading to the activation of neurodegenerative pathways (Barron and Pike, 2012; Gahete *et al.*, 2010; Grimm *et al.*, 2013). Increased oxidative stress in the AD brain is also an important factor decreasing the half-life of NEP and this process seems to be counteracted by some natural substances such as green tea extracts and polyphenols which trap free radicals (Ayoub and Melzig, 2006). Moreover, recent studies have shown a close relationship between NEP level in the CSF of AD patients and the extent or rate of neurodegeneration measured by brain amyloid load using PET exploration (Grimmer *et al.*, 2019).

The presence of A β oligomers in brain is a physiological mechanism but its chronic accumulation after several years of incubation is probably due to a disorder in its turnover rate. The clearance rate of brain A β varies from 7.6% per hour in controls to 5.2% per hour in AD (Maruyama *et al.*, 2005; Mawuenyega *et al.*, 2010). This process induces a toxic proteinopathy and the occurrence of amyloid plaques. It has been shown that the presence of high levels of A β oligomers in the extracellular spaces constitutes the initial toxic event that triggers the cascade of deleterious processes including neuronal damage, inflammatory response, apoptosis and brain atrophy leading to dementia (Kageyama *et al.*, 2018). A preferential localization of A β oligomers in the extracellular spaces has been demonstrated by microdialysis experiments, and the acute efficacy of therapeutic antibodies directed against A β confirmed this idea (Dodart *et al.*, 2002; Takeda *et al.*, 2013; Viola and Klein, 2015). Interestingly, it has been found that the increase of NEP synthesis decreases the abundance of brain A β oligomers in environmental enrichment conditions (Mainardi *et al.*, 2014). Furthermore, NEP is localized almost exclusively at the plasma membrane in direct contact with extracellular A β oligomers, insoluble fibrillars and amyloid plaques. (Whyteside and Turner, 2008). Therefore, pharmacology-based induction of NEP expression or gene therapy approach to increase brain NEP level may constitute promising

strategies to prevent or counteract cerebral A β accumulation. In particular, for the development of pharmacological strategies to induce brain NEP that significantly degrades A β peptides, various observations led us to believe that tryptophan and some of its metabolites belonging to the methoxy-indole pathway (5-HIAA and precursors) or to the kynurenine pathway (the neuroprotective kynurenic acid) may represent important or promising candidates. Indeed, several results argue for a critical role of 5-HIAA and KYNA in the turnover of NEP which plays an important part in the clearance of toxic A β peptides in late-onset AD (Klein *et al.*, 2013; Klein *et al.*, 2018).

The role of tryptophan

L-tryptophan is an essential amino-acid and the precursor of different metabolic pathways. The kynurenine pathway is dominant, while the synthesis of serotonin appears to be minor and in competition with the previous pathway. The kynurenine pathway is driven by TDO, which exists mainly in the liver, and by IDO, which is mainly expressed in the brain (Zadori *et al.*, 2018). Serotonergic neurons are present in two principal nuclei, the dorsal and the medial raphe, which project to multiple brain regions (brainstem, thalamus, hippocampus and cortex), while melatonin is synthesized from serotonin in the pineal gland. The majority of all these substances have been implicated in the pathophysiological and in AD symptoms (Rodriguez *et al.*, 2012).

Diets containing a high tryptophan content have been shown to improve learning and memory in AD, along with a concomitant change in the synthesis of 5-HT and 5-HIAA (Musumeci *et al.*, 2017; Noristani *et al.*, 2012). The modulation of serotonin neurotransmission by serotonin selective re-uptake inhibitors (SSRI) or 5-HT receptor ligands has been shown to modify the non-amyloidogenic processing of APP metabolites (Fisher *et al.*, 2016; Jin *et al.*, 2017). A high tryptophan diet increases hippocampal serotonergic fiber density and reduces A β accumulation in 3xTg-AD mice. The mechanism underlying this phenomenon is not yet elucidated but a role for serotonin is suspected.

Simultaneously, tryptophan is the precursor of neuroprotective (kynurenic acid, picolinic acid, NAD⁺) and neurotoxic metabolites (quinolinic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid) through the kynurenine pathway, which metabolizes more than 90% of tryptophan under

normal conditions (Platten *et al.*, 2019). The increase of tryptophan metabolism probably has an effect not only on trycat (tryptophan catabolites) of the methoxy indole pathway but also on kynurenine metabolites which are involved in the pathophysiology of neurodegenerative processes (Guo *et al.*, 2016). Thus, a high tryptophan diet appears beneficial for neuronal survival but the respective role of each trycat remains obscure.

The inter-related serotonin and kynurenine pathways

Tryptophan hydroxylase (TPH) is the rate-limiting step of serotonin synthesis and metabolism. The activity of TPH is influenced by several factors, including TPH gene expression and protein post-translational modification and degradation. TPH activity is also closely linked to the availability of its different substrates for hydroxylation, including dioxygen and tryptophan (Roberts and Fitzpatrick, 2013). The levels of these compounds determine the rate of serotonin production, but also the amount of both 5-hydroxytryptophan (5-HTP)(serotonin precursor) and 5-hydroxyindol-acetic acid (5-HIAA) (serotonin metabolite). Since TPH is strictly dependent on ferrous ions (Fe^{2+}) and is inactivated by ferric ions (Fe^{3+}), its activity is also reduced by reactive oxygen species (ROS) or iron deficiency.

Tryptophan has a pivotal role as a precursor for the activity of the two major pathways constituted by kynurenine and serotonin metabolism. For serotonin, its synthesis and availability is facilitated by tryptophan intake, with improved memory acquisition in rodents and decreased intraneuronal A β accumulation in the brain of 3xTg-AD animals. Both SSRI and increased dietary tryptophan intake reduce amyloid plaques and induce antidepressant effects in humans (Noristani *et al.*, 2012; Sun *et al.*, 2017).

Tryptophan availability also influences kynurenine synthesis (Zadori *et al.*, 2018). Important enzymes that control the synthesis of some neurotoxic derivatives of the kynurenine pathway are indoleamine 2,3 dioxygenase (IDO) and tryptophan 2,3 dioxygenase (TDO), which are induced by proinflammatory cytokines (e.g. IL-1 β , IL-2, IL-6, IFN- γ) (Souza *et al.*, 2017). A neuroinflammatory process is considered to precede, accompany and reinforce the toxic effects induced by abnormal production and/or clearance of aggregated proteins in several neurodegenerative diseases, with a particular importance in AD (Laurent *et al.*, 2018). Besides

the elevated levels of cytokines, the activation of Tau kinases and production of hyper-phosphorylated Tau participate in the inflammatory process, while the accumulation of amyloid peptides activates microglia and astrocytosis, with the participation of ROS and nitric oxide. A competitive process has been hypothesized between kynurenine and serotonin pathways (Keszthelyi *et al.*, 2012; Le Floc'h *et al.*, 2011). Thus, the occurrence of neuroinflammation and abnormal protein accumulation with energy metabolism/respiratory problems may be related to an imbalanced ratio between kynurenine and serotonin pathways leading to predominance of kynurenine toxic metabolites (Bohar *et al.*, 2015).

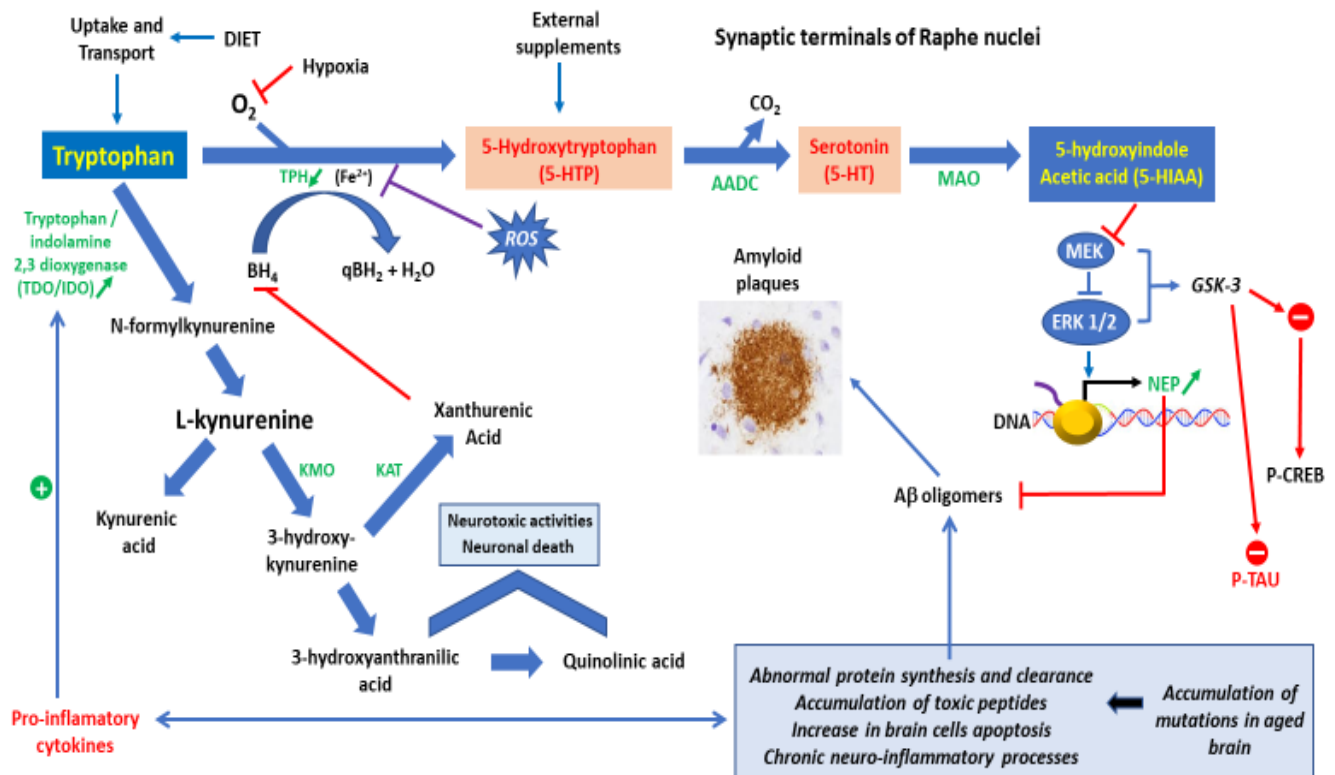


Figure 1: 5-HIAA, the end product of serotonin synthesis, which promotes NEP expression in brain, is dependent on tryptophan from the diet and gut metabolism, but also on TPH-2 activity in the brain. The activity of this enzyme is the rate-limiting step in serotonin and 5-HIAA production. Hypoxia, ROS and xanthurenic acid are known factors which could influence TPH activity. Neuroinflammation commonly present in AD brain induces IDO-1 and promotes

tryptophan conversion into metabolites belonging to the kynurenine pathway rather than the transformation of tryptophan into 5-HTP and serotonin.

The serotonin pathway, neprilysin and AD

Serotonergic projections emerge from several nuclei located in the dorsal midbrain and pons. Most of the serotonergic neurons belong to the dorsal raphe nucleus (DRN) which sends projections to the anterior part of the brain (cortex, hippocampus, striatum) but also to the brainstem and spinal cord. In vivo brainstem imaging has associated important changes in the DRN during early symptoms of AD-related dementia, with dramatic cell loss and cytoskeletal pathology consisting of phospho-tau neurofibrillary accumulation (Michelsen *et al.*, 2008; Rub *et al.*, 2000). These changes are thought to be the basis of non-cognitive and psychological symptoms of dementia consisting of detrimental serotonergic disturbances like depression, wake-sleep cycle modifications, loss of appetite, confusion and agitation (Lanctot *et al.*, 2001). In AD, the decrease in the number of 5-HT neurons is accompanied by a reduction in 5-HT and its metabolite 5-HIAA. However, most studies have focused on serotonin, its various receptors and the serotonin transporter. Chronic SSRI administration has been reported to reduce A β accumulation in some models of transgenic mice with APP/PS1 mutations. In fact, it is the general activation of serotonergic neurotransmission which appears to be beneficial for AD pathophysiology and symptomology. Therefore, the multiple receptors activated by serotonin have been actively studied in the context of AD (Meneses, 2017). The general increase in extracellular 5-HT should modulate the global activity of the entire family of these receptors with an imprecise cumulative result on serotonergic synaptic and extra-synaptic activities. The stimulation of 5-HT₁, 5-HT₂, 5-HT₄ receptor classes modulates the processing of amyloid protein precursor (APP) and the synthesis of A β peptides. By contrast, 5-HT₆ receptor antagonists improve cognitive performance in behavioral tests. Nevertheless, the impact of serotonergic receptors to ameliorate the disease is still under debate and study. The interest in a preventive process to avoid or decrease neuronal destruction and brain atrophy is fundamental and the hope to regenerate neuronal tissue appears to be a very optimistic view considering the near future.

The pharmacological regulation of the synthesis and elimination of A β peptides in the brain is considered one of the primary factors to protect the brain and avoid neuronal losses. NEP activity in brain, among other proteases endowed with a physiological role, is most probably regulated in a healthy brain. Apart from the close relationship between endogenous somatostatin (Burgos-Ramos *et al.*, 2008), NEP and A β , others compounds able to regulate NEP activity in brain are of pharmacological origin (Nalivaeva *et al.*, 2012a). But the variation of NEP activity with age and toxic peptides accumulation confirm the interest of a physiological regulation of its activity in the brain. Regarding this regulation, we explored recently the role of tryptophan derivatives acting as natural sensors for NEP activity.

We demonstrated that 5-HIAA, the final catabolite of serotonergic pathway with no identified functional activity in the brain, induces NEP expression in neuroblastoma cell culture and in the mouse brain *in vivo*. The EC₅₀ of NEP protein expression induced by 5-HIAA is within the concentration range of brain endogenous 5-HIAA, suggesting that 5-HIAA-induced brain NEP expression may constitute a natural regulatory mechanism occurring *in vivo* allowing the serotonergic system to maintain brain A β homeostasis. Interestingly, chronic treatment with repetitive administration of 5-HIAA (or precursor like 5-HTP) that significantly reduced brain A β in the transgenic APPSWE mouse model for AD and in the phosphoramidon-induced cerebral NEP inhibition mouse model, also ameliorated cognitive performance in APPSWE mice. Cellular and molecular evidence contributed to support a role of MEK/ERK pathway inhibition in the mechanism of action of 5-HIAA that seems to interact with the MAP-kinase pathway (Klein *et al.*, 2018).

Implication of the kynurenine pathway in A β degradation

Several studies are in favor of an up-regulation of the metabolism of tryptophan through the kynurenine pathway during the pathophysiological processes leading to AD (Kincses *et al.*, 2010). In particular, this up-regulation seems to play a role in the oxidative and neuroinflammation mechanisms that precede AD symptomology. However, the kynurenine metabolites can have either neurotoxic or neuroprotective effects (Deora *et al.*, 2017). Indeed, excitotoxicity may be related to the increase of 3-hydroxykynurenine (3-HK) and quinolinic acid

(QUIN) metabolites (Bonda *et al.*, 2010; Parrott and O'Connor, 2015) while the inhibition of 3-HK formation through the blockade of Kynurenine monooxygenase (KMO) has beneficial effects against neuronal/synaptic loss and memory deficits in mouse models of AD (Zwilling *et al.*, 2011). This inhibition favors the synthesis of the neuroprotector kynurenic acid (KYNA) which has been evidenced as an inducer of NEP (Klein *et al.*, 2013; Parrott and O'Connor, 2015). Interestingly, the decrease of 3-HK/KYNA ratio and the endogenous synthesis of KYNA in fruit flies are both neuroprotective (Breda *et al.*, 2016; Deora *et al.*, 2017). Therefore, even though the concentration of KYNA at the synapse and at glutamatergic ionotropic receptors is not precisely known, it seems reasonable to expect micromolar concentration of this compound in physiologically or pharmacologically induced situations. Thus, the role of KYNA in the regulation of NEP expression and maintenance of A β concentration represents an interesting track to explore for the development of strategies against A β accumulation and toxicity.

The metabolite QUIN, which appears to be of important toxicity, has been co-localized with A β and Tau in the AD brain (Breda *et al.*, 2016; Wu *et al.*, 2013). The concentration of QUIN is dependent on the activity of IDO/TDO that is activated by neuroinflammatory factors such as cytokines (IL-1 β , INF- γ) and glucocorticoids. By contrast, the inhibition of TDO, which induced an increase in tryptophan levels in *C. elegans*, led to neuroprotection (van der Goot *et al.*, 2012). Moreover, KMO inhibition has been reported as beneficial against AD pathophysiology. Indeed, this inhibition, decreases the concentrations of 3-HK and xanthurenic acid (XA)(3-HK metabolite) that significantly reduces the production of BH₄, a co-factor activating TPH which critically determines brain serotonin synthesis (Haruki *et al.*, 2016).

Altogether, the data available on tryptophan metabolism via the kynurenine pathway suggest that the development of neuroprotective strategies based on the activation of this pathway to reduce brain A β accumulation should take into account the possible neurotoxic effects of certain metabolites which must be inhibited in parallel.

NEP and peripheral tryptophan metabolites

A bi-directional effect between the gut microbiota and the activity of several brain neurotransmitters or neuromodulators has been established since many years and several

neuroactive compounds are known to be produced peripherally (O'Mahony *et al.*, 2015; Sarkar *et al.*, 2016). AD pathogenesis involves important metabolic pathways with multiple functional losses and neuronal death. The composition and activity of the gut microbiota may participate to brain A β accumulation, particularly via the modifications of 5-HT metabolism and trycates pathways (Agus *et al.*, 2018; Vogt *et al.*, 2017). We propose that some precursors of NEP-inducers including KYNA and 5-HIAA, produced in the gastrointestinal tract, may be responsible for the modulation of NEP activity in the brain. The blood brain barrier blocks the entrance of KYNA or 5-HIAA into the brain, but the permeability of this barrier is frequently altered during the incubation of AD for many years before occurrence of the symptomology (Nation *et al.*, 2019). However, KYNA or 5-HIAA precursors could penetrate the CNS, either freely or by regulated transport. Tryptophan, kynurenine or 5-HTP are produced by the intestinal microbiome and may influence the production of NEP inducers in a chronic manner (O'Mahony *et al.*, 2015). In these regards, NEP expression in the CNS could be regulated by the periphery and influence brain A β composition.

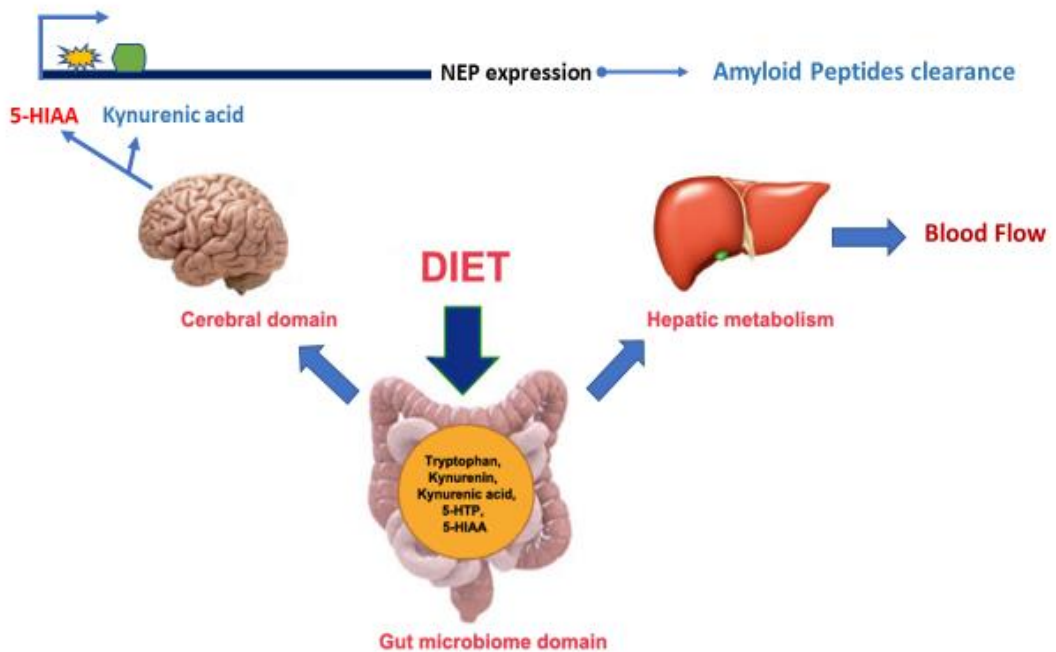


Figure 2: A possible role for gut microbiota and hepatic metabolism to produce tryptophan metabolites from diet precursors. Chronic synthesis of tryptophan metabolites in the intestinal domain could have a role in the induction of cerebral NEP during the preclinical period. This is in part due to the composition of diets and to intestine and blood-brain barrier permeabilities which might influence chronically brain NEP expression and take part in the control of A β accumulation.

AH receptor and MMP activation through tryptophan metabolism

The extracellular matrix is a complex and dynamic structure made mostly of proteoglycans and glycoproteins. This compartment of the CNS is modified and continuously rebuilt to maintain and adapt the structure, plasticity and support for intercellular activities. Remodeling of these processes supposes in part the action of several proteases, including serine proteases and matrix metalloproteinases (MMP)(De Stefano and Herrero, 2017). This last class of enzymes represents a family of more than 28 members including MMP-2 and MMP-9 (gelatinases) that are present in large quantity in the brain (Chopra *et al.*, 2019). The accumulation of these enzymes secreted by astrocytes and microglia are stimulated by the increase of amyloid peptides (A β 1-40 and 1-42) in the extracellular spaces accompanied by an enhancement of inflammatory processes. This contributes to changes in the permeability of the blood brain barrier, in the cleavage of amyloid oligomers and in the clearance of toxic peptides (Yan *et al.*, 2006; Yin *et al.*, 2006). The neurofibrillary tangles made of Tau aggregation are also degraded by MMP-3 and MMP-9 activities (Mizoguchi *et al.*, 2009; Nubling *et al.*, 2012). The role of MMPs in the pathogenesis of AD is further supported by the increased expression of these enzymes in post-mortem brain tissue of AD patients. Both MMP-2 and MMP-9 are also over-expressed in astrocytes surrounding senile plaques in AD transgenic mice brain (APP/PS1 and APPswe) (Yan *et al.*, 2006; Yin *et al.*, 2006).

The extracellular architecture and composition under the control of MMP and other proteases (plasmin) is regulated in part by the aryl hydrocarbon receptor (AhR) which is a ligand-activated transcription factor (Hillegass *et al.*, 2006). Several xenobiotics, but also endogenous tryptophan metabolites participate in the regulation of this receptor activity. Stimulation of the AhR

pathways alters the expression of several extracellular matrix proteins and modifies cellular adhesion (Kung *et al.*, 2009). MMP's members of the protease families have been shown to be targets of the AhR pathway and are activated by ligands of this nuclear receptor (Murai *et al.*, 2018). AhR *-/-* mouse embryo fibroblasts show a reduction in MMP-2 activity. Neuroinflammatory cytokines (IL-6, IL-22) are involved in the activation of AhR and of some MMP in different phases of AD. In addition, several endogenous AhR activators are derived from indole or tryptophan metabolism (Murray and Perdew, 2017; Platten *et al.*, 2012). Nanomolar concentrations of KYNA increase Ahr-dependent genes and IL-6 under inflammatory conditions. Xanthurenic acid (XA), Kynurenine and cinnabarinic acid (CA) have also been identified as endogenous AhR agonists and are possible inducers of MMP involved in AD pathophysiology. Apart from these brain endogenous tryptophan metabolites, several AhR ligands are derived from the intestinal microbiota (Hubbard *et al.*, 2015). The metabolism of tryptophan by the gut ecosystem is the source of numerous ligands for AhR. Serotonin has recently been identified as an AhR activator in the intestinal mucosa (Manzella *et al.*, 2018). Indole-3-acetic acid and tryptamine generated by commensal bacteria have also been shown to stimulate AhR. Therefore, despite the fact that potential deleterious actions of AhR ligands are suspected in inflammation, immune regulation and cancer propagation (Bock, 2019), it may be of interest to investigate the role of AhR ligands deriving from tryptophan metabolism in the activation of MMP to reduce brain A β load in AD or MCI patients (Chopra *et al.*, 2019; Kaminari *et al.*, 2017; Leake *et al.*, 2000; Stix *et al.*, 2001). Indeed, the activities of AhR ligands in brain A β homeostasis as well as the functions of endogenous kynurenine and serotonin metabolism appear as a possible strategy to adapt the clearance system during proteinopathy-induced disorders.

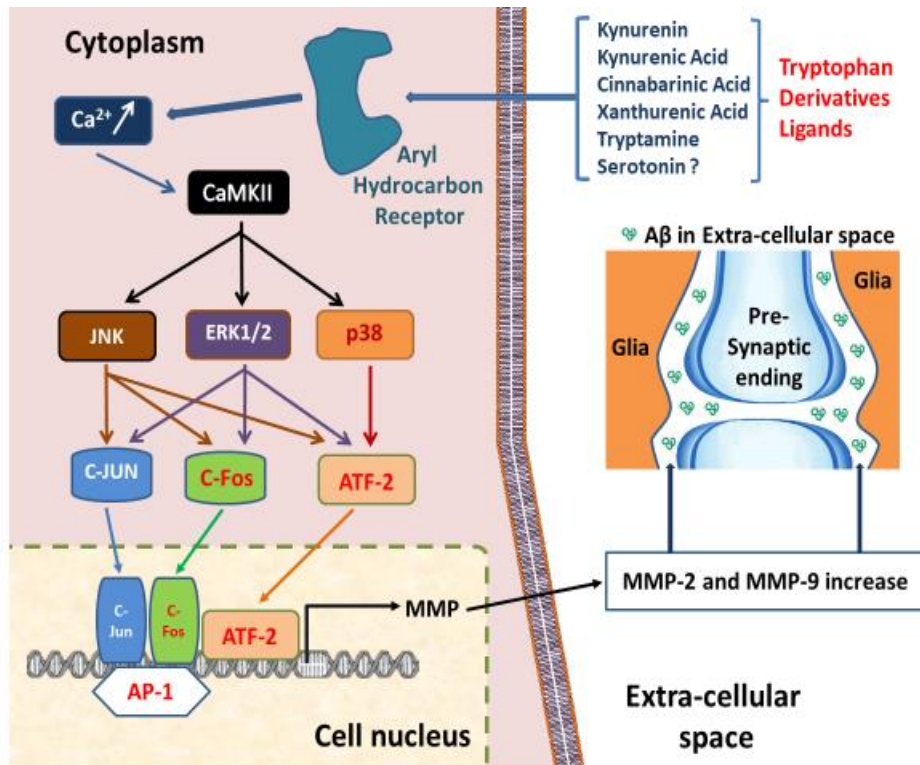


Figure 3. Several signaling pathways can be stimulated by the activated form of Ahr which is expressed in many tissues. Ahr has multiple functions in maintaining cellular homeostasis and disease (Larigot *et al.*, 2018). Several tryptophan metabolites induce Ahr-dependent genes and pathways, including tryptophan metabolites synthesized in the skin or in the gut microbiota. The induction of CYP1A1 by serotonin has recently been described. Among the genes upregulated by Ahr signaling are the neo-expression of MMP1, MMP2 and MMP9. This process appears to proceed via non canonical Ahr pathway through calcium and calmodulin kinase II as reported for airway diseases (Monteiro *et al.*, 2008; Tsai *et al.*, 2014). We propose a similar mechanism in the brain and a role for Ahr/MMP in the control of the extracellular space composition and clearance of Aβ. Tryptophan metabolites, natural ligands of Ahr, could have a major role in this process.

Concluding remarks Our results showing the induction of NEP expression by 5-HIAA and KYNA support a regulatory role of tryptophan metabolites on A β accumulation in the brain (Klein *et al.*, 2013; Klein *et al.*, 2018). KYNA is known for its neuroprotective activity but 5-HIAA was until now considered as a dead-end product of serotonin metabolism with no functional role. Both compounds depend on the availability and metabolism of tryptophan whose increase through diet induced beneficial effects in AD mice models. Because neuroinflammation is a long-term process that precedes and follows the toxic proteinopathy and abnormal brain A β peptide turnover in AD, it may be interesting that future works thoroughly investigate the eventual interactions of 5-HIAA and KYNA with neuroinflammatory mechanisms. Indeed, it has been shown that chronic inflammation causes the channeling of tryptophan degradation through the induction of IDO that promotes the kynurenine pathway (Zadori *et al.*, 2018). This phenomenon may explain, at least in part, the reduction of serotonergic activity in the raphe nuclei and the decrease of 5-HIAA production in brain serotonergic terminals. Consequently, this process may reduce brain NEP activity leading to A β peptide accumulation as evidenced in AD. Moreover, the present review interestingly reveals that, because the potentiation of kynurenine pathway stimulates the synthesis of excitotoxic compounds such as 3-HK and QUIN that are deleterious for brain cell survival, the administration of Kynurenine and KMO inhibition, which increase KYNA concentrations and block 3-HK and XA production, may promote NEP over-expression. Therefore, the sporadic neo-expression of NEP during short periods to reduce brain A β accumulation can be considered as a preventive approach against AD neurotoxic process. Because some kynurenine and serotonin derivatives, including melatonin, are considered beneficial agents to decrease brain A β oligomer accumulation, it could be interesting to use combinatory pharmacological tools to deplete in repeated sessions abnormal increase of cerebral A β concentrations. The combination of 5-HTP per os to potentiate 5-HIAA formation (Jacobsen *et al.*, 2016), but also of kynurenine + KMO inhibitor to stimulate KYNA synthesis may be of interest to prevent or to delay as much as possible the occurrence of AD symptomology.

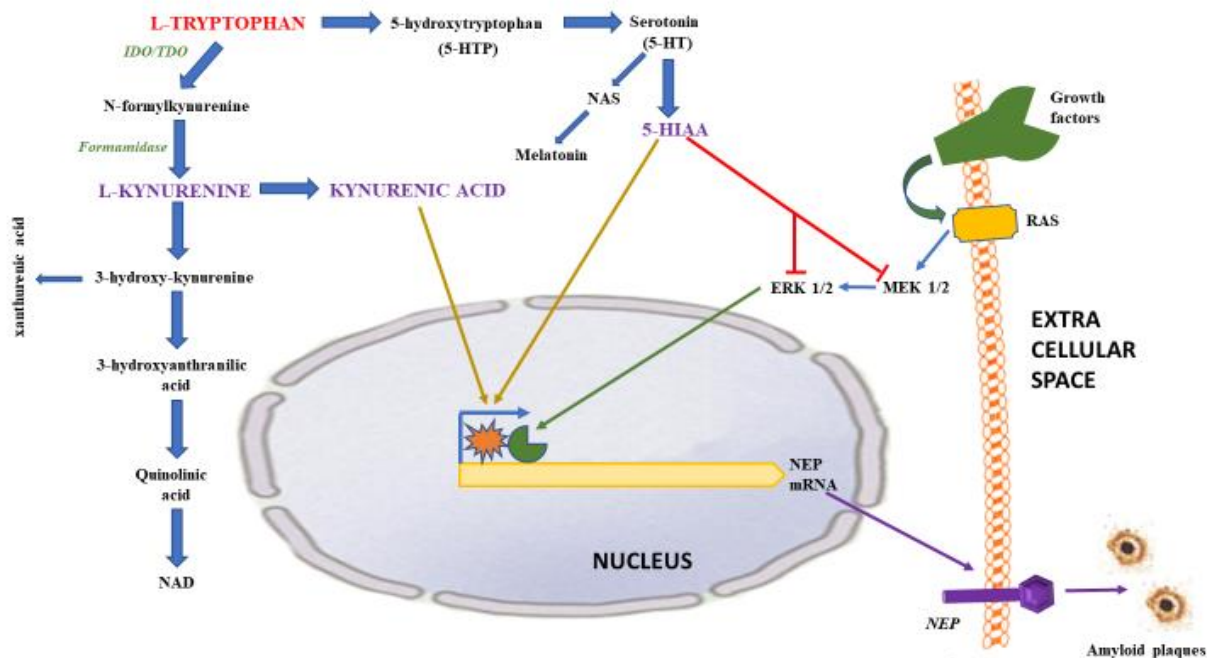


Figure 4: In the AD brain, the serotonergic activity is depleted due to the alteration of Raphe Nuclei and 5-HIAA stimulatory action on NEP expression is strongly reduced. In the same time, pro-inflammatory cytokines may potentiate IDO and the kynurenine pathway, leading to the synthesis of neurotoxic compounds 3-HK and QUIN but also to the production of KYNA. Interestingly, because KYNA is an inducer of NEP activity and expression, KYNA may contribute to reduce the potential deleterious effects of 3-HK and QUIN. In order to increase the beneficial effect of KYNA, its cerebral concentration could be enhanced by the administration of its precursors (tryptophan and kynurenine) or by the inhibition of KMO which blocks kynurenine conversion into 3-HK.

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