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Aryl hydrocarbon receptor in glia cells: A plausible glutamatergic neurotransmission orchestrator

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Abstract

Glutamate is the major excitatory amino acid in the vertebrate brain. Glutamatergic signaling is involved in most of the Central Nervous System functions. Its main components, namely receptors, ion channels, and transporters, are tightly regulated at the transcriptional, translational, and post-translational levels through a diverse array of extracellular signals, such as food, light, and neuroactive molecules. An exquisite and well-coordinated glial/neuronal bidirectional communication is required for proper excitatory amino acid signal transactions. Biochemical shuttles such as the glutamate/glutamine and the astrocyte-neuronal lactate represent the fundamental involvement of glial cells in glutamatergic transmission. In fact, the disruption of any of these

coordinated biochemical intercellular cascades leads to an excitotoxic insult that underlies some aspects of most of the neurodegenerative diseases characterized thus far. In this contribution, we provide a comprehensive summary of the involvement of the Aryl hydrocarbon receptor, a ligand-dependent transcription factor in the gene expression regulation of glial glutamate transporters. These receptors might serve as potential targets for the development of novel strategies for the treatment of neurodegenerative diseases.

Keywords Aryl hydrocarbon receptor; radial glia; glutamate transporters; Kynurenic acid, Circadian rhythms.

Declarations

Ethical Approval Not applicable.

Competing interests The authors declare no competing interests.

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1 Introduction

L-Glutamate (Glu) is considered the main excitatory amino acid neurotransmitter in the vertebrate Central Nervous System (CNS). It is involved in most of the brain functions including learning, memory, cognition, proliferation, and migration among others [1]. During development, glutamatergic signaling plays a crucial role in the correct formation of dendritic spines and synapses [2, 3]. Glu released from presynaptic neurons activates both ionotropic (GRI) and G-protein- coupled Glu metabotropic receptors (GRM) expressed in neurons and glial cells, [4-7], see Table 1. A tight control of Glu extracellular levels is mediated by a family of sodium-dependent plasma membrane Glu transporters known as excitatory amino acid transporters. Five Glu transporters have been characterized thus far, excitatory amino acid transporter 1 (EAAT1/Na⁺-dependent glutamate/aspartate transporter (GLAST)), EAAT2/glutamate transporter 1 (GLT1), EAAT3/excitatory amino acid carrier 1 (EAAC1), EAAT4, and EAAT5. EAAT1 and EAAT2 are mainly expressed in astrocytes and are responsible for more than 80% of the Glu synaptic cleft clearance [8]. Glutamatergic transmission is an example of a tripartite synapse since glial Glu transporters are responsible for the recycling of this neurotransmitter. The impairment of Glu uptake results in a neurotoxic insult due to the over activation of extra-synaptic Glu receptors [9, 10], specifically of the N-methyl-D-aspartate subtype (GRIN) containing the 2B subunit (GRIN2B) [11] in a process known as excitotoxicity. Over the years, it has been considered that excitotoxicity is the biochemical framework of several neurodegenerative diseases [12].

Table 1 GR in glial cells function

Effect	GR involved	Model	Reference
Ca ²⁺ responses evoked by Glu	GRMI / GRMII	Rat hippocampal slices	[13]
Decrease <i>glast</i> mRNA levels and GLAST activity <i>via</i> YY1	GRIA, GRIK	Chick Bergmann glia primary cultures	[14, 15]
Currents evoked by Glu	GRIA, GRIN	Mouse cortical astrocytes slices and isolated cells	[16]
Increases in p70 ^{S6K} phosphorylation	GRIK, GRM1	Chick Bergmann glia primary cultures	[17]
Increase in p-eEF2 and eEF1A phosphorylation	GRIA, GRIK	Chick Bergmann glia primary cultures	[18, 19]
Deficits in motor performance in Erasmus Ladder	GRIA1, GRIA4	Lacking double inducible knockout GRIA1 GRIA4	[20]

		Mouse Bergmann glial cells	
Increases BMAL1 protein levels	GRMI, GRIA	Chick Bergmann glia cells primary culture	[21]
Ca ²⁺ currents	GRIA, GRIN	Mouse periglomerular astrocytes	[22]

2 Glial cells in glutamatergic transmission

The term *glial cells* include all non-neuronal cells distributed throughout the Nervous System. The subtypes of glia in the CNS are oligodendrocytes, ependymal cells, microglia, and astrocytes. Astrocytic cells are as abundant as neurons in the human adult brain, although the ratio between astrocytes/neurons depends on the brain area analyzed [23, 24]. In particular, in the primate and rodent cerebral cortex, astrocytic cells outnumber neurons, while in the cerebellum, neurons outnumber astrocytes [25-27].

Historically, glial cells have been considered only as support structures, but nowadays, it is evident that astrocytes intervene in diverse CNS functions. Astrocytes participate in the genesis and elimination of synapses, enhance synaptic transmission, and are involved in calcium and potassium homeostasis, among other functions. Moreover, these cells provide metabolic support to neurons through the *so-called* astrocyte-lactate-neuronal shuttle [24, 28-34]. Lactate seems to have implications in neurons that go beyond metabolic support *i.e.*, inducing the expression of *c-fos*, *zinf268*, and *arc* genes via the activation of GRIN [35]. Interestingly, astrocytes are involved in the generation of circadian rhythmicity, modulating extracellular Glu levels, a process in which EAATs are involved, as has been elegantly described in the mice Suprachiasmatic Nuclei (SCN) [36]. Moreover, glial Glu signaling through both receptors and transporters contributes to gene expression regulation and glial-neuronal interactions [16-18, 37, 38] summarized in Table 1.

An example of a well-characterized tripartite synapse is the cerebellar parallel fiber-Purkinje cell synapse and between Müller, bipolar and ganglion cells in the retina [39, 40]. Bergmann glial cells (BGC) completely wrap this glutamatergic synapse and are responsible for Glu removal through GLAST/ EAAT1 [39]. Once in the glial cell, Glu is metabolized to Glutamine (Gln) by the glia-enriched, Gln synthetase (EC 6.3.12), then Gln is released from the glial compartment to the presynaptic neuron through the sodium-dependent neutral amino acid transporters (SNATs). Gln is deaminated in the neuronal compartment by glutaminase (EC 3.5.1.2), converted back to Glu, and packed into synaptic vesicles in order to be released after an action potential [41, 42] The coupling among Glu uptake and Gln glial release [43, 44] and the metabolic Glu recycling constitutes the previously mentioned Glu/ Gln shuttle. Moreover, a GLAST/EAAT1-dependent glucose uptake in these cells has also been reported [45].

3 Glutamate Receptors

Glu receptors are classified into two groups: metabotropic (GRM) and ionotropic (GRI) receptors. GRM are G protein-coupled receptors that have been classified in terms of their sequence homology into three groups: Group I, formed by GRM1 and GRM5, Group II comprising GRM2, GRM3 and GRM4. Finally, GRM6, GRM7, and GRM8 belong to Group III.

The expression of most of the GRM mRNAs has been detected in glial cells, GRM3 and GRM5 have been detected in hippocampal astrocytes. Secondary cortical astrocytes express GRM1 and GRM5 [46, 47]. Functional GRM1/GRM2 are present in rat hippocampal astrocytes [13, 48] see Table 2. Nevertheless, GRM signaling properties remain unclear. Apparently, there is a cell type-dependent signal cascade [49, 50].

Table 2 Glial GR

Receptor detected	Model	Reference
GRIA1, GRIA3, GRIA4 mRNA	Bergmann and Müller glial cells-chick	[51]
GRM3, GRM5 mRNA	Rat Hippocampal astrocytes	[46]
GRM1, GRM5 protein	Rat secondary cortical astrocytes	[47]
GRIN1, GRIN2B, GRIN2C mRNA	Mouse Cortical astrocytes	[52]
GRIN1, GRIN2A, GRIN2B mRNA and protein	Mouse Cortical astrocytes	[53]
GRIK1, GRIK2, GRIK4, GRIK5 mRNA GRIK2 protein	Mouse neopallia astrocytes	[54]
GRIK4 protein	Rat Hippocampal astrocytes	[55]
<i>Gria1, Gria2, Gria3, Gria 4</i>	Cerebellar Astrocytes cerebellum, neocortex and hippocampus-mouse	[56]

In contrast, ionotropic receptors were subdivided before their molecular characterization was accomplished. Three different pharmacological distinct GRI have been described: 5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartate (NMDA), and Kainate (KA) receptors. Their respective subunits are, for AMPA receptors: GRIA1, GRIA2, GRIA3, GRIA4., NMDA: GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, and KA: GRIK1, GRIK2, GRIK3, GRIK4, GRIK5 [57]. Glu receptors are expressed in neurons and glial cells, in

the latter, ionotropic and metabotropic groups have also been reported to be expressed throughout the CNS, and to be functionally active (Table 1 and 2) [7, 16, 24, 58].

KA receptors (GRIK) are tetramers with a homomeric or heteromeric composition [59]. GRIK1-3 are low-affinity subunits required for ion channel functionality, and as a consequence, can form homomeric receptors, in contrast, high-affinity subunits (GRIK4-5) only form heterodimeric ion channels [60]. The pharmacological and kinetic properties of KA channels depend on their specific subunit composition [61]. GRIK are activated by Glu, kainic acid, domoic acid, and AMPA ($EC_{50} \approx 50, 5$ and $0.3, 200 \mu\text{M}$) [62]. GRIK-specific antagonists include γ -D-glutamyl amino methyl sulphonic acid (GAMS), (3S,4aR,6S,8aR) -6- ((4-carboxy phenyl) methyl) -1,2,3,4,4a,5,6,7, 8,8a-deca hydro isoquinoline -3-carboxylic acid (LY382884), while 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) can also block AMPA receptors [63-65]. GRIK can mediate synaptic responses, in general terms, their synaptic current is smaller than those of GRIA, and their deactivation kinetics is slower [66]. In terms of Glu release, GRIK can exhibit a bidirectional modulation in the mossy fiber to CA3 synapse; at nanomolar KA concentrations, it increases Glu release while higher KA concentrations it diminishes Glu release [60, 66]. Concerning GRIK plasma membrane regulation, the Ca^{2+} /calmodulin-dependent kinase II (CaMKII) phosphorylates GRIK5 in S589, S892, and T976, increasing the receptors lateral mobility [67]. GRIK interacts with diverse membrane proteins; postsynaptic density protein 95 (PDS-95) was one of its first described partners [67]. The Ca^{2+} /diacylglycerol-dependent protein kinase (PKC) phosphorylates GRIK2 at S846, and S868, restricting its traffic [60].

AMPA receptors (GRIA) are ensembled as homo or heterotetramers [68], that can be activated by Glu, AMPA, quisqualate, and (RS)-2-amino-3-[3-hydroxy-5-(2-methyl-2H-tetrazol-5-yl)isoxazol -4-yl] propionic acid (2-Me-Tet-AMPA), with an EC_{50} of $296 \mu\text{M}$, $66.2 \mu\text{M}$, $16.3 \mu\text{M}$, and $3.4 \mu\text{M}$, respectively [69]. GRIA activation and deactivation kinetics are fast (millisecond range) and exhibit a strong desensitization [64]. GRIA heterotetramers are conformed by GRIA1 and GRIA2 subunits in CA1 hippocampal neurons, but their subunit composition is dependent on the brain area analyzed [70, 71]. GRIA N-terminus is extracellular, while the C-terminal domain is an intracellular component that provides a scaffold for post-translational modifications and protein interactions [72]. GRIA1 subunit plays a role in the activity of receptors at synapses through its C-terminal phosphorylation by CAMKII, protein kinase C (PKC), or the cyclic AMP-dependent protein kinase (PKA). Moreover, interaction with synaptic scaffold proteins containing a PDZ domain leads to the recruiting and retention of GRIA1 and GRIA2 at synapses during long-term potentiation processes [70, 73]. Within the plasma membrane, GRIA interacts with the Discs large homologs (DLG), DLG-1 or synapse associate protein 97 (SAP97) which binds to GRIA C-terminus and is associated with receptor trafficking, SPD-95, and SPD-93 binds to GRIA [74]. The formation of the transmembrane AMPA Receptor regulatory protein (TARP)/GRIA complex is necessary for the channel function, providing different physiological properties and intervening receptor trafficking [74].

The kinetics of the activation of NMDA receptors (GRIN) is slower than that of GRIA and GRIK, between ten and thousand milliseconds [64], the ligand-gated NMDA ion channel requires a strong depolarization to remove the external Mg^{2+} block and allow Ca^{2+} influx for an efficient activation, therefore it can also be considered as a voltage-dependent channel [75-77]. Moreover, GRIN activation requires the binding of two co-agonists; Glu and glycine (Gly), the latter acting as an activation modulator [78, 79]. GRIN are conformed by heterotetramers, each formed by at least one GRIN1 subunit and a combination of the others. The structural peculiarity of GRIN confers its diverse kinetic and pharmacological properties [80, 81]. Therefore, the outcome of GRIN activation depends on the subunit composition. For instance, GRIN2A-containing receptors activation has been associated with cell survival, while GRIN2B subunit activation results in cell death signaling [82]. Also, intracellular C-terminal GRIN2B signaling contributes to the excitotoxic response [11]. Most GRIN are assembled of GRIN1/GRIN2A or GRIN1/GRIN2B subunits [83]. GRIN2B-containing receptors are mostly enriched in extra-synaptic sites [84, 85]. Gly and other endogenous ligands of GRIN such as Quinolic acid (QUINA) and Kynurenic acid (KYNA), which are metabolites from tryptophan from the kynurenic pathway, modulate its actions *e.g.* QUINA acts as an agonist [86] and KYNA as an antagonist (EC_{50} 10 μ M) acting on the glycine-binding site [87, 88]. KYNA also is an antagonist of both GRIA and GRIK [89].

4 Glu Transporters

Extracellular Glu levels are regulated by a family of plasma membrane sodium-dependent Glu transporters named Excitatory Amino Acid Transporters (EAAT1-5) [3, 90]. The molecular characterization of these transporters was reported in the early 90's: EAAT1; *slc1a3*; glutamate/aspartate transporter (GLAST), EAAT2; *slc1a2*; glutamate transporter 1 (GLT1), EAAT3; *slc1a1*; excitatory amino acid carrier 1 (EAAC1), EAAT4; *slc1a6* and EAAT5; *slc1a7* [8, 91-96]. Each Glu molecule is co-transported with three Na^+ and one H^+ with one K^+ ion efflux [97, 98] the transport is electrogenic and dependent on the Na^+ gradient. EAAT1/GLAST is functional and physically coupled with the Na^+/K^+ ATPase [99] and the neutral amino acid transporter 3 (SNAT 3) [43]. Glu transporters are expressed differentially in specific brain regions, for example, EAAT1/GLAST is enriched in the cerebellar cortex, in Bergmann glia cells, retinal Müller glial cells, while EAAT3 and EAAT4 are expressed in Purkinje cells. In other brain structures, EAAT2/GLT1 is highly enriched in glia cells [3, 100-102]. EAAT1/GLAST is the major transporter expressed in the cerebellum [3, 101]. This transporter is present in high levels during early development in most of the encephalon, while EAAT2/GLT1 expression is increased during development, which explains GLAST use in immunohistochemistry as a marker of glial cells [103]. Glial Glu transporters are critical for a proper regulation of extracellular Glu levels, preventing its spillage to the extra synaptic space, and by these means avoiding excitotoxicity [9, 10] and are apparently necessary for proper brain development. Cortical neurons maturation is impaired in the cortex of double mutant GLAST-/-

/GLT1^{-/-} mouse model [104]. Furthermore, Glu transporters participate in Glu signaling in glial cells [38] and in circadian rhythms generation *i.e.* using a competitive non-transportable EAATs blocker reduces the amplitude and robustness of PER2::LUC oscillations in explants from suprachiasmatic nuclei [36]. On the other hand, GLAST and GLT-1 mRNA levels are decreased in the *gyrus frontalis medialis* from sporadic Alzheimer's disease donors [105].

A wide variety of mechanisms regulate Glu transporter function and gene expression; including gene transcription, translation, and traffic to the plasma membrane [106, 107]. Different molecular mechanisms participate in the regulation of each transporter [108] *e.g.* concerning *chglast* promoter, the Ying-Yang 1 (YY-1) transcription factor represses its expression of chicken GLAST [15]. While NF- κ B acts as a positive regulator [109]. AMPA receptors activation decreases GLAST/EAAT1 mRNA and protein levels through PKC activation [14], see Table 1. Dibutyryl cAMP (dbcAMP) up-regulates GLAST/EAAT1 mRNA, protein levels and transport activity Dibutyryl cAMP (dbcAMP), that activates PKA [110-113]. Moreover, EAAT1/GLAST protein levels and activity might be regulated by clock factors; its promoter contains functional E-boxes [114] and its expression is decreased in *Per2* mutant mice [115], indicating a circadian influence in its regulation. Estrogens are involved in EAAT2/GLT1 regulation through Estrogen Receptor (ER) activation and increased binding activity of the CREB and NF- κ B transcription factor to EAAT2/GLT1 promoter [116-118].

5 The Kynurenic Pathway

Over 95% of dietary Tryptophan (TRP) is metabolized by the Kynurenic pathway (KP). A reduced amount of TRP is used in protein synthesis and the serotonin pathway [86]. Indoleamine-pyrrole 2,3-dioxygenase (IDO1) is an important limiting enzyme of this pathway [119]. In primary cultures of mouse brain astrocytes IDO1 mRNA has been detected through RT-PCR after treatment with interferon- γ [120]. Metabolites produced through the KP present in the vertebrate CNS at nanomolar concentrations [121]. IDO1 is expressed in primary cultures of neurons, microglia and astrocytes derived from mixed brain human fetuses. Likewise, its mRNA and protein have been detected in mouse primary astrocytic cultures. Moreover, QUINA also was found in these cultures [122, 123]. In the KP, modulator molecules are generated: as previously mentioned, KYNA and QUINA, act as GRI modulators, act as an antagonist for GRIA, GRIK, and GRIN and agonists for GRIN, respectively (see section 3). On the other hand, some metabolites of KP - Kynurenine (KYN), KYNA, and QUINA - also are ligands for the aryl hydrocarbon receptor (AHR) Fig. 1 (see section 8, Table 3 for details).

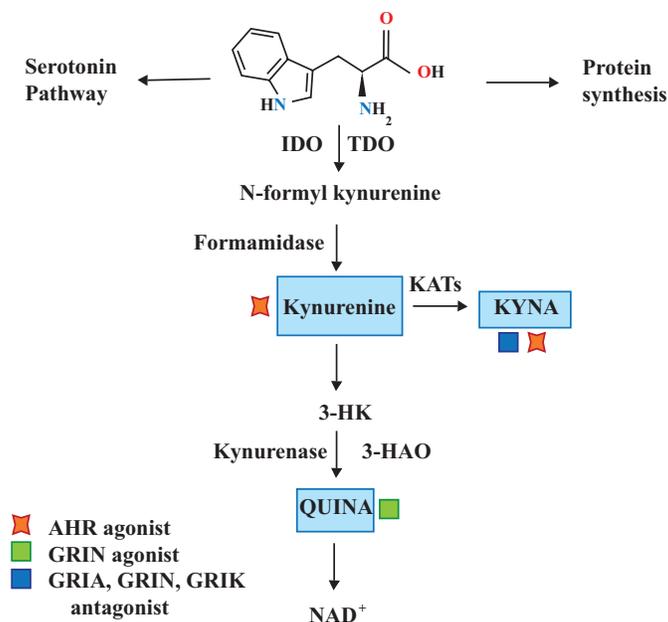


Fig. 1 *KP*. Indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO) Kynurenine aminotransferases (KATs) 3-hydroxykynurenine (3-HK), kynurenic acid (KYNA), quinolic acid (QUINA), aryl hydrocarbon receptor (AHR). For details of GRI modulators / AHR ligands (See text section 3 and Table 3). Modified from [124]

Table 3 Endogenous and Exogenous AHR ligands

	Ligand	Affinity	Reference
	Kynurenic acid	100 nM	[125]
Endogenous	Kynurenine	4 μ M	[126]
	FICZ	0.07 nM	[127]
Exogenous	TCDD	0.27 nM	[128]
	B[a]P	0.5 μ M	[129]
	β -Naphthoflavone	20 nM	[130]

6 AHR in CNS: Expression and function

The AHR is a ligand-dependent transcription factor that belongs to the basic helix-loop-helix family (bHLH) with a Per-Arnt-Sim (PAS) domain [131, 132]. Present in the cytoplasm as an inactive complex, AHR is expressed in brain homogenates of different species including mammals, rodents, and birds [133, 134]. In mice, it is expressed in specific CNS regions including the cerebral cortex, cerebellum, hippocampus, olfactory bulb, and in retinal photoreceptor cells [135, 136]. Furthermore, in rats, AHR mRNA is expressed in the olfactory

bulb, ventral tegmental area, hippocampus, caudal arcuate nucleus, *raphe nucleus* and the *globus pallidus* [137]. AHR and ARNT (Aryl hydrocarbon nuclear translocator) protein levels from mouse cerebellum homogenates were examined by immunoblot analysis between postnatal day (PND) 0–PND21, revealing that AHR protein levels decrease throughout development [138]. Moreover, relevant to glutamatergic transmission, AHR is expressed in murine and human astrocytes [139-142] (Table 4). It is relevant to mention that AHR is expressed in a glioblastoma cell line from human brain [126, 143, 144].

Table 4 AHR expression in neurons and astrocytes

Expression	Preparation	Specie	Reference
Protein	Cerebellar granule neuroblasts	Mouse	[138]
mRNA, Protein	Cortical neurons -Primary culture	Rat	[140]
mRNA	Cortical astrocytes -Primary culture	Mouse	[141]
Protein	Cortical astrocytes –Primary culture	Mouse	[139]
mRNA, Protein	Cortical astrocytes-Primary culture	Mouse	[145]
Protein	Astrocytes co-localization AHR- GFAP hippocampal <i>post-mortem</i> tissue	Human	[142]

Historically, AHR has only been studied in regard to the metabolism and detoxification of environmental pollutants and was originally described as a xenobiotic receptor. With the development and use of AHR knockout models [146, 147], pharmacological approaches and the discovery of endogenous ligands, its physiological role has begun to be unveiled. Recently, in an AHR-*null* mouse model it has been reported that this receptor participates in the regulation of KP, modulating protein levels of kynurenine aminotransferase II and the levels of KYNA; in this model both are increased in the cortex and striatum [148]. Moreover, AHR activity participates in the development of contextual fear memory. Absence of this receptor induces alteration of granule cell morphology, decrease of mushroom spines density, increase of total dendritic length, and decrease in the GRIA/GRIN ratio in dentate gyrus granule cells [149, 150]. It has a role in gaze stabilization at the eye movement, since the optokinetic reflex is decreased in the AHR *-/-* mice [151]. AHR also might act as an environmental stress sensor for the retina since its invalidation leads to alterations similar to age-related macular degeneration [152]. Interestingly, AHR takes importance in circadian rhythm regulation, given the fact that in an AHR *+/-* mice model, *Per2* mRNA and protein levels are enhanced within the SCN [153].

AHR is involved in neuronal migration and dendritic development of olfactory interneurons [154] as well as in the survival and differentiation of hippocampal neurons [149]. AHR also modulates the expression of some GRIN subunits [155] and the neurogenesis of cerebellar granule cells [156]. In addition, through the use of specific AHR antagonists, it was established that this receptor is involved in cerebellar granule cells' apoptotic processes induced by xenobiotic insults [157]. All of these properties are not exclusively neuronal; for example, in primary astrocyte cultures from wild type or AHR deficient mice, expression of the Chemokine (C-C motif) ligand 2 (*Ccl2*), Colony-stimulating factor 2 (*Csf2*), Nitric oxide synthase 2 (*Nos2*), is increased in a model of experimental autoimmune encephalomyelitis [141]. The endogenous physiology of AHR is complex and the involved mechanisms remain unclear.

7 Canonical and non-canonical activation pathway

In the canonical AHR activation pathway, the AHR-ARNT complex is recruited to a specific DNA-response element (5'-TNGCGTG-3') known as xenobiotic responsive element (XRE) or Dioxin responsive element (DRE) to control the transcription of its target genes [158] like cytochrome 1A1 (*cyp1a1*), the AHR repressor (*ahrr*), indoleamine-pyrrole 2,3-dioxygenase (*ido1*), [159, 160]. This receptor senses extra and intracellular signals from endogenous and foreign origin [91]. As mentioned earlier, AHR inactive complex is localized in the cytoplasm and is composed of the chaperone proteins heat shock protein 90 (Hsp90), prostaglandin E synthetase 3 also known as p23 protein, AHR interacting protein (AIP), also called ARA9 or HVB X-associated protein 2 (XAP-2), and the non-receptor protein tyrosine kinase or pp60^{src} [161, 162]. Once AHR is bound by an agonist it is dissociated from the cytoplasmic inactive complex and is translocated to the nucleus to interact with the ARNT or with the hypoxia-inducible factor 1- β (HIF1 β) [163]. AHR can interact with other transcription factors, in a non-canonical pathway. For example, AHR can be associated with RelB, forming an NF- κ B subunit. The newly formed complex binds to the DNA sequence 5'-AGATGAGGGTGCATAAGTTC-3' named RelBAHRRE. It is especially relevant the GGCTCCAT sequence immersed in and, this the GGCTCCAT sequence encompasses regulating expression of IL-8, which regulates the expression of genes like IL-8 [164]. Another AHR non-canonical pathway involves formation of a complex with the Estrogen Receptor (ER)-AHR (ERAHR), disrupting the ER signaling [165]. On the other hand, through immunoprecipitation assays, an interaction between AHR and BMAL1 was evidenced, acting as a repressor of *Per1* expression [166]. Furthermore, AHR-ARNT complex can block the transcription of certain ER-regulated genes at least in part by the AHR ARNT complex binding to its DNA recognition sequence and disrupting ER signaling (see Fig. 2 [167, 168]). Moreover, AHR can interact with and activate the Mitogen-Activated Protein Kinase (MAPK) [169, 170]. In this review, we embark on the possibility of AHR as a possible orchestrator of glutamatergic neurotransmission, Fig. 3.

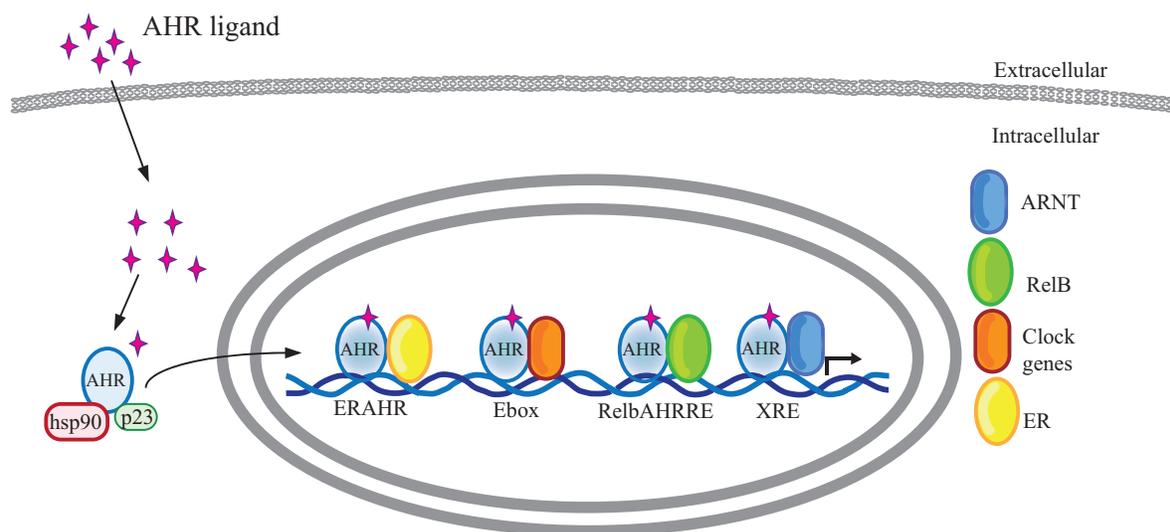


Fig. 2 *AHR Canonical and non-canonical pathways.* AHR through non-canonical pathway is capable of physically associating with components responsible for circadian rhythmicity, hormone disruption, and dysregulation of gene transcription; BMAL1

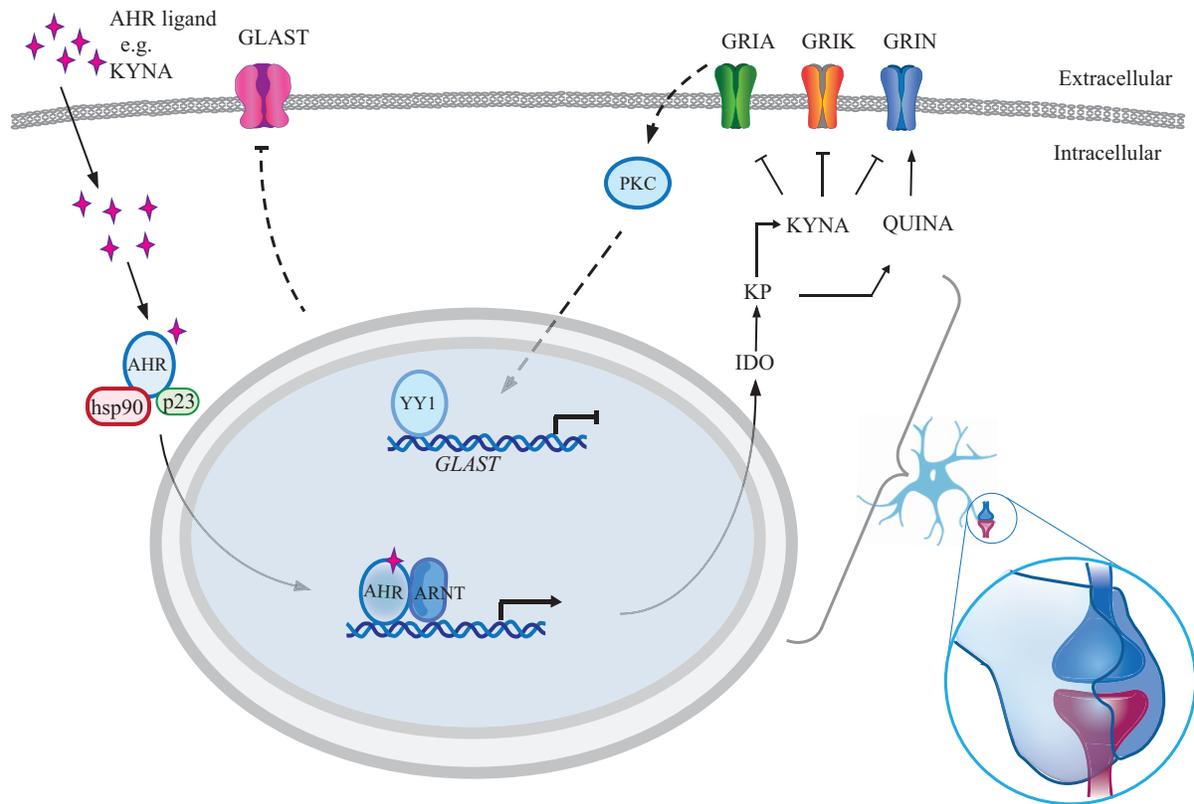


Fig. 3 *Glial AHR as an orchestrator in glutamatergic neurotransmission.* A canonical AHR gene regulated is IDO, limiting in KYNA an AHR ligand and a GR antagonist, Table 3 section 3, and 5. Antagonize GRIA downregulate *chglast*, table 2, section

8 Ligands

AHR ligands can be classified as endogenous or exogenous. The exogenous ligands come from the diet and are tryptophan metabolites produced by the KP, including some photoproduct tryptophan-derivates such as 6-formylindolo- [3,2-b] -carbazole [171] (Table 4). Exogenous or xenobiotics AHR ligands usually are environmental toxins *e.g.* polycyclic aromatic hydrocarbons or polychlorinated biphenyls [171]. Dioxins are persistent organic pollutants, that were used during the Vietnam War, known as the *agent orange*. The most important dioxin and exogenous AHR ligand is 2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD [128]. It is a

ubiquitous environmental pollutant presenting neurotoxic effects and was classified as a human carcinogen by the WHO [161, 172, 173], The model molecule used to study polycyclic aromatic hydrocarbons is the Benzo[*a*]Pyrene, which has been described as an exogenous AHR ligand [129] with potential neurotoxic and glutamatergic actions (Table 4).

9 Effects of the exposure to AHR ligands in glutamatergic transmission

As can be easily understood, plasma membrane Glu binding proteins (receptors and transporters) play a fundamental role in the regulation of glutamatergic transmission. Decreased levels of Glu receptors are linked to deficits in learning and memory processes. Moreover, diminished mRNA or protein levels of Glu transporters have been observed in amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and other neurodegenerative diseases. [57, 174, 175]. The AHR endogenous ligand KYNA acts as GRIN and GRIK antagonist while QUINA is an agonist for GRIN. Nevertheless, the characterization of the effect of AHR activation on Glu transporters and receptors is far from complete (see Table 5). In any event, it has been demonstrated that Glu receptor agonists do not alter [³H]-D-aspartate uptake, but AMPA and KA receptor antagonists decrease it [³H]-D-aspartate uptake [176] impacting on the regulation of expression and function of Glu transporter GLAST [14], Table 2. It has also been described, through siRNA AHR knockdown strategies, that downregulation of AHR results in diminished *grin2a* RNA levels and increased *grin2b* mRNA levels in neonatal rat cortex primary neuronal cultures [155], supporting the idea that AHR is a modulator of different components in the glutamatergic neurotransmission. In Fig. 3 we provide a schematic modulatory representation of this interplay.

Table 5 Effects of exogenous ligands on glutamatergic components

Effect	Model	Ligand	Reference
↓ mRNA GRIN2B Prefrontal cortex and Hippocampus	C57BL/6J mice	B[<i>a</i>]P 2.5 y 6.25 mg/kg intraperitoneal Twice per week for 90 days	[177]
↓ mRNA GRIN2B Brain cortex	Rat PND 100	B[<i>a</i>]P 3 mg/kg <i>in utero</i> exposure GD 14-17 oral gavage	[178]
	female Balb/c mice (18-20 g)	B[<i>a</i>]P 0.02, 0.2, 2, 20, 200 mg/kg intraperitoneal daily	[173]

↓ mRNA GRIN2B		for 11 days	
Cerebellum, hippocampus,			
↓ mRNA GRIN2A			
Hypothalamus			
↑ mRNA GRIN2A			
Prefrontal cortex			
↓ GRIN2B protein			
Cerebral cortex	Rat PND 45	TCDD 100 and 700 ng/kg on GD 15 oral gavage	[179]
↑ mRNA GRIN2A			
Neocortex	Rat PND 45 800 ng/kg		
Hipocampus		TCDD 200 ng/kg and 800 ng/kg single dose on GD 15 oral gavage	[180]
↓ mRNA GRIN2B			
Neocortex	PND 5 and 45 200 ng/kg and 800 ng/kg		
Hippocampus			
↓ [³ H] glutamate uptake			
Cerebral cortical slices	Rats PND 14 and 60	TCDD 700 ng/kg single dose on GD18 oral gavage	[181]
↓ GLT-1 protein			
	C6 cells	TCDD 10 nM for 12 h	[182]

10 Conclusion

Glutamatergic transmission is involved in most brain functions and its regulation is fundamental for the organism and its interactions with the environment. Glial cells participate in Glu mediated-transactions, being

responsible for its recycling and thus the maintenance of this neurotransmitter system. Multiple signaling molecules are capable of interfering with this exquisite and precise control. A plausible involvement of AHR is suggested by the evident after the described participation of the clock genes in regulation of glial Glu transporters. Certainly, in the next few years, more information regarding the role of this important transcription factor in brain health and disease will be unveiled.

Abbreviations:

AHR: Aryl hydrocarbon receptor. AHRR: Aryl hydrocarbon repressor. AIP: AHR interacting protein. ALS: Amyotrophic lateral sclerosis. ARNT: Aryl hydrocarbon nuclear translocator. B[a]P: Benzo [a] Pyrene. PND: Postnatal day. BGC: Bergmann Glial cells. BMAL1: Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocator-Like Protein 1. 2-Me-Tet-AMPA: (RS)-2-amino-3-[3-hydroxy-5-(2-methyl-2H-tetrazol-5-yl)isoxazol -4-yl] propionic acid. 3-HK: 3-hydroxykynurenine. CAMKII: Calcium/calmodulin-dependent protein kinase II. CLOCK: Circadian Locomotor Cycles Kaput. CNQX: 6-cyano-7-nitroquinoxaline-2,3-dione. DRE: Dioxin responsive element. EAAC1: Excitatory amino acid carrier 1. EAAT: Excitatory amino acid transporter. ER: Estrogen receptor. FICZ: 6-formyl- indole [3,2-b] carbazole . GAMS: γ -D-glutamyl amino methyl sulphonic acid. GD: Gestational day. GLAST: Glutamate/ Aspartate transporter. Gln: Glutamine. GLT1: Glutamate transporter 1. Glu: L-Glutamate. CNS: Central Nervous System. HIF1 β : hypoxia-inducible factor 1- β . Hsp90: Heat shock protein 90. KP: Kynurenic pathway. KYN: Kinurenine. IDO: Indolamine- pyrrole -2,3-deoxygenase. KYNA: Kynurenic acid. LY382884: (3S,4aR,6S,8aR)-6-((4-carboxyphenyl)methyl)-1,2,3,4,4a,5,6,7, 8,8a-decahydroisoquinoline-3-carboxylic acid. MAPK: Mitogen Activated Protein Kinase. mRNA: messenger ribonucleic acid. NMDA: N-Methyl-D-Aspartate. P23: Prostaglandin E synthetase 3. PKA: Protein kinase A. PKC: Protein kinase C. QUINA: Quinolinic acid. SCN: Suprachiasmatic nucleus. SCN: Suprachiasmatic Nuclei. SNAT: Neutral amino acid transporter. TCDD: 2,3,7,8-tetraclorodibenzo-p-dioxin. TDO: tryptophan-2,3-deoxygenase. KATs: Kynurenine aminotransferases. Xap2: X-associated protein 2. XRE: Xenobiotic responsive element.

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