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REVIEW

Xanthurenic acid: A role in brain intercellular signaling

Michel Maitre¹  | Omar Taleb¹ | H el ene Jeltsch-David^{1,2} | Christian Klein¹ | Ayikoe-Guy Mensah-Nyagan¹

¹Biopathologie de la My el ine, Neuroprotection et Strat egies Th erapeutiques, INSERM U1119, F ed eration de M edecine Translotionnelle de Strasbourg (FMST), Universit e de Strasbourg, B atiment CRBS de la Facult e de M edecine, Strasbourg, France

²Biotechnologie et signalisation cellulaire, UMR 7242 CNRS/Universit e de Strasbourg, Illkirch Cedex, France

Correspondence

Michel Maitre, Biopathologie de la My el ine, Neuroprotection et Strat egies Th erapeutiques, INSERM U1119, F ed eration de M edecine Translotionnelle de Strasbourg (FMST), Universit e de Strasbourg, B atiment CRBS de la Facult e de M edecine, 1 rue Eug ene Boeckel, 67000 Strasbourg, France.
Email: maitre@unistra.fr

Abstract

Xanthurenic acid (XA) raises a growing multidisciplinary interest based upon its oxidizing properties, its ability to complex certain metal ions, and its detoxifier capacity of 3-hydroxykynurenine (3-HK), its brain precursor. However, little is still known about the role and mechanisms of action of XA in the central nervous system (CNS). Therefore, many research groups have recently investigated XA and its central functions extensively. The present paper critically reviews and discusses all major data related to XA properties and neuronal activities to contribute to the improvement of the current knowledge on XA's central roles and mechanisms of action. In particular, our data showed the existence of a specific G-protein-coupled receptor (GPCR) for XA localized exclusively in brain neurons exhibiting Ca²⁺-dependent dendritic release and specific electrophysiological responses. XA properties and central activities suggest a role for this compound in brain intercellular signaling. Indeed, XA stimulates cerebral dopamine (DA) release contrary to its structural analog, kynurenic acid (KYNA). Thus, KYNA/XA ratio could be fundamental in the regulation of brain glutamate and DA release. Cerebral XA may also represent an homeostatic signal between the periphery and several brain regions where XA accumulates easily after peripheral administration. Therefore, XA status in certain psychoses or neurodegenerative diseases seems to be reinforced by its brain-specific properties in balance with its formation and peripheral inputs.

KEYWORDS

dopamine, glutamate, neurodegeneration, neuropsychiatric diseases, neurotransmission, xanthurenic acid

1 | INTRODUCTION AND BACKGROUND

Xanthurenic acid (XA) is an intermediate of the kynurenine pathway (KP), whose presence in the brain comes from the local metabolism of tryptophan (Trp) from the diet and gut microbiome. Its precursor, 3-HK comes from the metabolism of kynurenine via kynurenine

monooxygenase (KMO), which governs the balance between KYNA and XA. These two compounds are closely related structural analogs (see [Figure 1](#)).

Until now, XA has not aroused much interest, especially at the CNS level. It has often been presented as a detoxification factor of 3-HK, considered neurotoxic (Ostapiuk & Urbanska 2022), complexing certain

Abbreviations: 3-HK, 3-hydroxykynurenine; AhR, aryl hydrocarbon receptor; BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; EPSP, excitatory postsynaptic potential; FICZ, 6-formylindolo-carbazole; GC-MS, gas chromatography-mass spectrometry; GPCR, G-protein-coupled receptor; GTP, guanosine-5'-triphosphate; IDO1, indolamine 2,3 dioxygenase; I.P., intra-peritoneal; KAT, kynurenine aminotransferase; KMO, kynurenine monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; LATS, large neutral amino acid transporters; NAAG, N-Acetyl-Aspartyl-Glutamate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NMDA, N-methyl-D-aspartate; OAT, organic anion transporter; PFC, prefrontal cortex; QUIN, quinolinic acid; ROS, reactive oxygen species; SN, substantia nigra; TDO, tryptophan 2,3 dioxygenase; TH, tyrosine hydroxylase; Trp, tryptophan; TTX, tetrodotoxin; VTA, ventral tegmental area; XA, xanthurenic acid.

BOX 1 XA induces metal-chelate complexes

XA easily forms coordination complexes with transition metals (iron, zinc) that accumulate with age and can contribute to the development of neurodegenerative diseases by altering the permeability of the BBB (Kubicova et al., 2019). Reduced tissue levels of XA can lead to chemical changes increasing the amount of reactive oxygen species (ROS) causing long-term pathological disorders in many organs, including the CNS, with the accumulation of iron in amyloid plaques (Lovell et al., 1998). XA would inhibit the peroxidation of several compounds, including lipids and DNA. At the neuronal level, it has been shown that the presence of zinc participates in an XA-Zn complex that promotes the transport and reversible binding of XA (Gobaille et al., 2008). Recent results have shown, in *Drosophila*, that XA is a major ligand for zinc and plays an important role in its homeostasis, indicating the importance of the KP in immune contexts related to age and neurodegenerative problems (Garay et al., 2022). Zinc is an essential element for brain function with involvement in the stabilization of structures, many catalytic reactions and synaptic transmission (Jomova et al., 2022; Long et al., 2022).

metals such as copper or zinc (see Box 1) Garay (Garay et al., 2022), or participating in the formation of ocular cataracts (Malina et al., 2002). More recently, the role of XA has been described in the dissemination of tumor cells in certain glioblastoma lines (Varricchio et al., 2023).

It is considered a group II metabotropic glutamate receptor agonist and a competitive inhibitor of glutamate vesicular transporters (Bartlett et al., 1998; Copeland et al., 2013; Fazio et al., 2015, 2017; Neale et al., 2013, 2014). Changes in XA levels in the serum of some psychotic patients have been described (Curto et al., 2019; Oxenkrug et al., 2019; Skorobogatov et al., 2023) as well as in patients with bipolar disorder (Bartlett et al., 1998; Bartoli et al., 2021; Copeland et al., 2013; Curto et al., 2019; Fazio et al., 2015, 2017; Neale et al., 2013, 2014; Oxenkrug et al., 2019; Skorobogatov et al., 2023).

2 | PART OF THE XA IS SYNTHESIZED IN BRAIN FROM TRP

XA is produced by the metabolization of Trp in the microbiome and mainly in the brain. XA can also come from the diet for a little part.

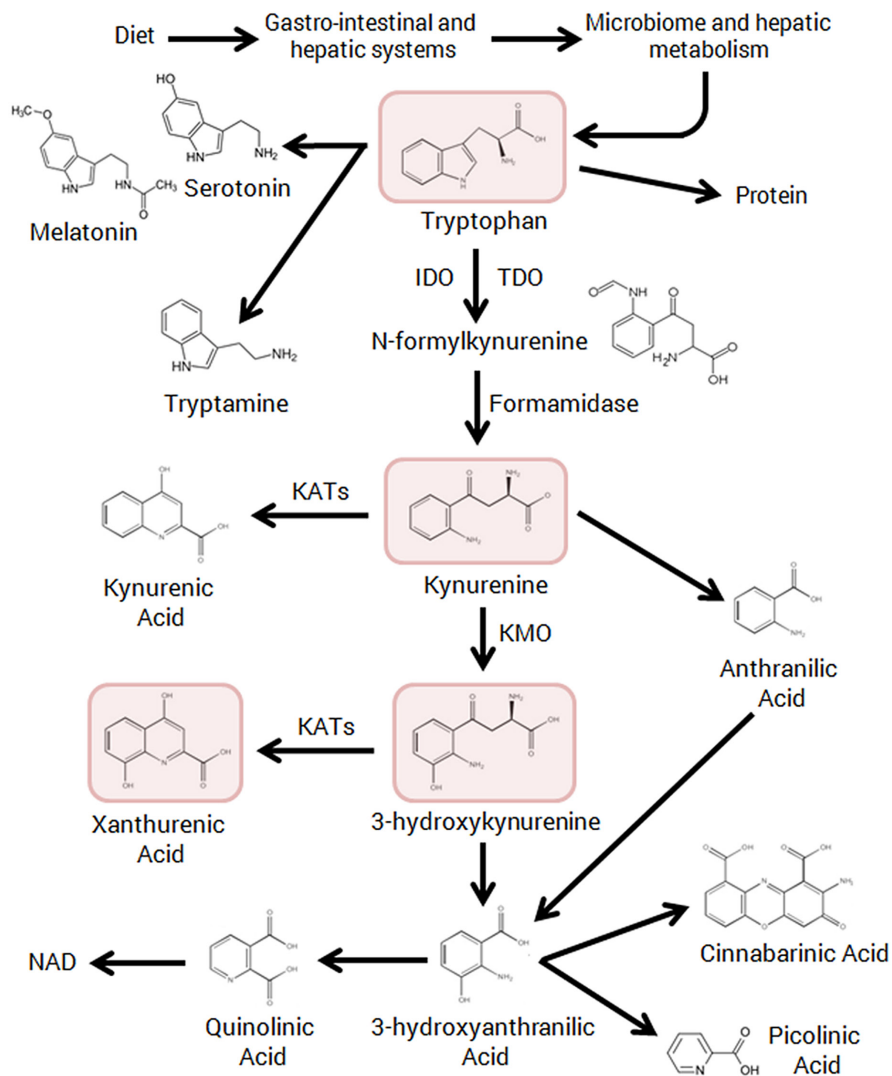
Trp is an essential amino acid for humans only provided by food. About 95% of Trp is catalyzed by tryptophan 2,3 dioxxygenase (TDO) or indolamine 2,3 dioxxygenase (IDO1), which are distributed in several peripheral organs. TDO is the main enzyme involved in regulating Trp levels in the blood, and therefore its concentrations in the brain (Klaessens et al., 2022). Trp is released, transformed, and

metabolized in various circuits expressed by the intestinal microbiome, and transported through the fluctuating permeability of the intestinal wall (Roth et al., 2021). All these compounds enter the brain to varying degrees through membrane transporters of variable specificities and according to the permeability of the blood-brain barrier (BBB). The bioavailability of Trp in the brain is an essential factor for the regulation of serotonin, melatonin, and tryptamine synthesis, in competition with the KP that accounts for about 90–95% of Trp degradation (Gao et al., 2020). Variations in the respective activities of these different metabolic pathways are suspected to be responsible for a wide variety of neurological and psychiatric problems (Li et al., 2022). The liver TDO is mainly responsible for the catabolism of the Trp which participates in the regulation of its turnover. IDO1 in peripheral tissues is primarily under the control of immune responses and inflammation (Klaessens et al., 2022). All these mechanisms can have an influence on the central nervous system (CNS) through the bioavailability of Trp and its kynurenic ring catabolites, most of which have neuroactive properties. The bacterial population of the intestinal tract may influence specific brain functions through this mechanism (Wiedlocha et al., 2021).

Trp enters the brain and neurons through the neutral amino acid transporter that is also expressed by astrocytes and microglia. It is still possible that the organic anion transporter1/organic anion transporter3 (OAT1/OAT3), which carry KYNA and XA in relation to their brain concentration, may be affected (Uwai & Honjo, 2013). KP includes several metabolites that have an important pathophysiological role in many brain functions. Among these, KYNA is one of the most studied since it displays antagonistic properties at glutamatergic receptors (Bratek-Gerej et al., 2021; Stone, 2021). Its close relative is XA that is synthesized from 3-HK after hydroxylation of the latter by KMO and transamination mainly by kynurenine aminotransferase II (KAT II; Figure 1). KMO belongs to the NADPH-dependent flavin monooxygenase family and has aroused a lot of interest since it is the essential step for the synthesis of the neurotoxic compounds of KP, 3-hydroxyanthranilic acid, and quinolinic acid (QUIN). KMO also regulates the synthesis of 3-HK, which is the direct precursor of XA. Many KMO inhibitors have been synthesized and inhibition of this enzyme displays a beneficial effect on the course of certain neurodegenerative diseases. Reduction of KMO activity in the brain increases KYNA concentrations but also decreases 3-HK and XA levels not only in neurons but also in some peripheral tissues. These two last modifications could also have their roles in the neuroprotection described after KMO inhibition, in addition to the reduction of QUIN synthesis (Phillips et al., 2019). KMO is acutely dependent on energy activity and brain oxygenation because its activity requires good tissue oxygenation and NADP/NADPH. KMO activity has long been described as exclusively localized in microglia, but recent results have shown that much of this activity is contained in neurons in adult mice (Laumet et al., 2017).

From 3-HK, the last step of XA synthesis is driven by KATs. Arbitrarily, four different enzymatic activities (I, II, III, and IV) are identified as capable of synthesizing KYNA (Rossi et al., 2019). Several studies have shown that the mechanisms of formation of

FIGURE 1 Regulation of XA synthesis: XA as a metabolite of the kynurenine pathway. Tryptophan in the diet, modified by the intestinal microbiome and metabolized by the liver, is the source of many important metabolites including serotonin, melatonin, and tryptamine and gives rise to the kynurenine pathway. Highlighted in red are the main intermediates leading to XA, derived from 3-HK produced by KMO. 3-HK, 3-hydroxykynurenine; IDO, indoleamine-pyrrole 2,3-dioxygenase; KAT; kynurenine aminotransferase; KMO, kynurenine monooxygenase; KYNA, kynurenic acid; QUIN, quinolinic acid; NAD, nicotinamide adenine dinucleotide; TDO, tryptophan dioxygenase; XA, xanthurenic acid.



this compound from kynurenine and those leading 3-HK to XA are identical and part of a conventional transamination requiring a derivative of vitamin B6 as a cofactor. The transformation of 3-HK into XA is irreversible. KAT I is also glutamine transaminase, KAT II is also aminoacidate aminotransferase, KAT III glutamine transaminase and KAT IV mitochondrial aspartate aminotransferase. Kynurenine aminotransferase type II is the main transaminase that metabolizes 3-HK into XA, and several results have described the presence of this enzyme not only in astrocytes but also in various interneurons of the brain and in Purkinje cells of the cerebellum (Balog et al., 2021). In the latter structure, KAT II is absent from astrocytes. Recently, a specific localization of KAT II in neurons was evidenced in mice (Balog et al., 2021; Heredi et al., 2017).

XA and KYNA have several similar but sometimes also opposite functions in different areas. Often presented in the past as a detoxification factor with antioxidant functions (see Box 1), the functional importance of XA has recently been re-evaluated (Mithaiwala et al., 2021; Sathyaikumar et al., 2017). Our objective is to summarize the currently described properties of XA in the nervous system, its neuronal localization, and its modalities of extracellular release leading to a specific membrane response. The existence of a specific

GPCR for XA recognizing a synthetic antagonist argues for a role in intercellular signaling in the CNS. Furthermore, in partnership with KYNA, XA could participate in the regulation of dopaminergic influence and may play a role in the pathophysiology of certain neuropsychiatric diseases. We hypothesize that this system could be the target of ligands of therapeutic interest (Okuno et al., 2011; Taleb et al., 2021; Tufvesson-Alm et al., 2018; Venkatesan et al., 2020).

2.1 | The regulation of XA synthesis may occur in many steps

Little is known about the regulation of XA synthesis in the brain. First, the bioavailability of Trp via its dietary intake and the intestinal microbiota, its brain uptake via specific transporters, and its distribution in its various processing pathways probably plays a decisive role (Davidson et al., 2022; Fukuwatari, 2020; Li et al., 2022). In this regard, the role of melatonin in the serotonin synthesis circuit would participate in the balance between the synthesis of the neurotransmitter and the synthesis of kynurenine, a precursor of XA via 3-HK (Li et al., 2017).

The next important step on the route for XA synthesis is IDO1 not present in the liver unlike TDO (Dolsak et al., 2021). IDO's activity depends on a panel of inflammatory stimuli that increases the synthesis of kynurenine, but nothing is known about the consequences on the level or turnover of the XA compartment (Huang et al., 2020; Modoux et al., 2021; Platten et al., 2019). Considered as the limiting enzyme for kynurenine formation, IDO is expressed in the brain, especially in neurons, where its activity is potentiated by interferon-gamma and other lipopolysaccharide-induced cytokines (Roy et al., 2005). This enzyme belongs to the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-dependent flavin monooxygenase family and has aroused a lot of interest since it is the essential step for the synthesis of the neurotoxic compounds of KP, 3-hydroxyanthranilic acid, and quinolinic acid. KMO also regulates the synthesis of 3-HK, which is the direct precursor of XA. Many KMO inhibitors have been synthesized and inhibition of this enzyme displays a beneficial effect on the course of certain neurodegenerative diseases (Hughes et al., 2022). Reduction of KMO activity in the brain increases KYNA concentrations but also decreases 3-HK and XA levels not only in neurons but also in some peripheral tissues. These two last modifications could also have their roles in the neuroprotection described after KMO inhibition, in addition to the reduction of quinolinic acid synthesis (Phillips et al., 2019). KMO is acutely dependent on energy activity and brain oxygenation because its activity requires good tissue oxygenation and NADP/NADPH. KMO activity has long been described as exclusively localized in microglia, but recent results have shown that much of this activity is contained in neurons in adult mice (Laumet et al., 2017).

From 3-HK, the last step of XA synthesis is driven by KAT. Arbitrarily, four different enzymatic activities (I, II, III, and IV) are identified as capable of synthesizing KYNA (Rossi et al., 2019). Several studies have shown that the mechanisms of formation of this compound from kynurenine and those leading 3-HK to XA are identical and part of a conventional transamination requiring a derivative of vitamin B₆ as a cofactor. The transformation of 3-HK into XA is irreversible. KAT I is also glutamine transaminase, KAT II is also aminoadipate aminotransferase, KAT III glutamine transaminase and KAT IV mitochondrial aspartate aminotransferase. Kynurenine aminotransferase type II is the main transaminase that metabolizes 3-HK into XA, and several results have described the presence of this enzyme not only in astrocytes, but in various interneurons of the brain and in Purkinje cells of the cerebellum (Balog et al., 2021). In the latter structure, KAT II is absent from astrocytes. Recently, a specific localization of KAT II in neurons was evidenced in mice (Balog et al., 2021; Heredi et al., 2017).

In summary, the entire XA synthesis chain from Trp has a neuronal localization, even if this distribution is not exclusive. The presence of XA itself has been identified in neurons (Roussel et al., 2016). At many stages of this synthesis pathway, the regulation of XA production can be modulated and adapted from the neuronal capture of Trp through the fluctuation of IDO, KMO, and KAT's activities.

3 | XA AND ITS METABOLIC PATHWAY ARE PRESENT IN BRAIN NEURONS

We showed that brain XA levels can be altered after intra-peritoneal (I.P.) administration in rodents, without apparent behavioral or clinical disturbances, even after repeated injections in a subchronic mode (Taleb et al., 2021). Recently, it was demonstrated that XA passes the BBB and binds heterogeneously in brain tissue, indicating an uptake and metabolism of this compound that depends on the CNS regions concerned. In adult rats, XA endogenous concentrations were measured by gas chromatography–mass spectrometry (GC–MS) with a detection limit of approximately 50 picomoles/g fresh tissue. Concentrations in the richest regions were around 1 μM, while most other brain areas were at concentrations between 0.1 and 0.4 μM (Gobaille et al., 2008). Other regions have undetectable concentrations but an active turnover of XA cannot be excluded with low absolute levels of XA. At the cellular and subcellular levels, while the other main intermediates of the kynurenine cycle are present in glial cells, XA is localized in neurons, more precisely in somato-dendritic regions, and seems to be absent in axons (Roussel et al., 2016; Figure 2).

By contrast, the structural analog KYNA of the XA is known to be unable to penetrate the brain from the periphery. It is known that alterations in the metabolism or composition of the gut microbiome that participate in the release or synthesis of these compounds can modify certain brain functions and behaviors (Pu et al., 2022; Vadaq et al., 2022).

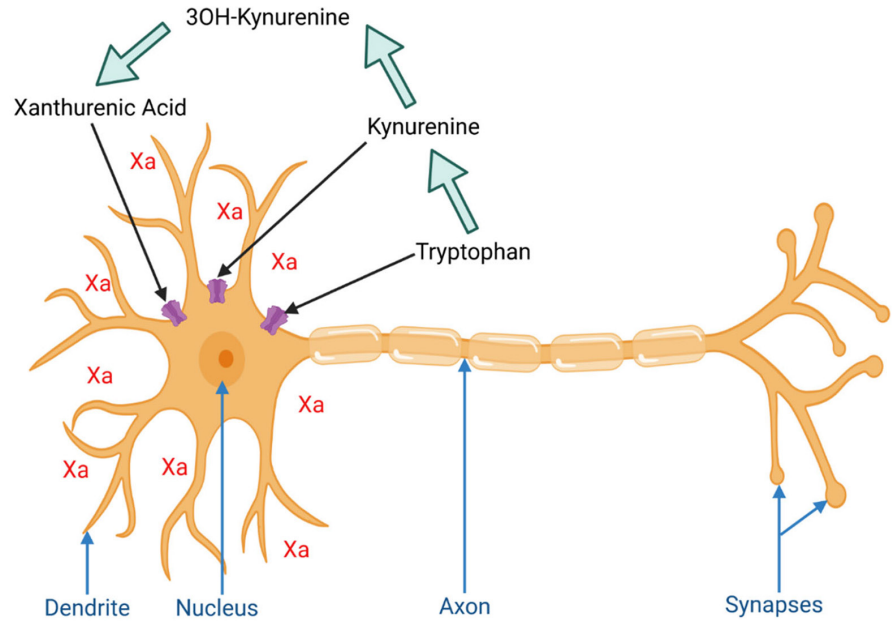
3.1 | XA exhibits a specific distribution, transport, accumulation, and release in brain

Several arguments support the existence of a metabolic circuit expressed by many neurons transforming Trp into XA. The latter compound has been identified exclusively in neurons of mice brain regions, such as the cortex, cerebellum, striatum, as well as in neurons from primary mouse cell culture. At the subcellular level, XA appears to be compartmentalized especially in the somatodendritic regions of the cell (Roussel et al., 2016).

Compared to the transport of KYNA, little work has been devoted to the uptake of XA. On neurons in culture (differentiated NCB-20), a Km of about 100 μM was determined. This capture is dependent on the presence of Zn²⁺ or Cu²⁺ ions, extracellular physiological concentrations of NaCl, and it is reduced by the presence of deoxyglucose illustrating the role of energy metabolism. In the same way, XA is captured by a preparation of synaptic vesicles with a Km of about 3 mM with a strong dependence on the presence of ATP and MgCl₂, blocked by the presence of 100 nM bafilomycin (Gobaille et al., 2008; Taleb et al., 2012).

Like KYNA, it is unlikely that the crossing of the BBB by XA passes through the large neutral amino acid transporters (LATs). More likely is the role of the organic anion transporters OAT1 and

FIGURE 2 In rodents, the cellular localization of XA appears to be exclusively somato-dendritic (in yellow). In the rat PFC, Ca^{2+} -dependent release of XA could be demonstrated *in vivo*. All the enzymes acting in the synthesis of XA are present in the neuron and transporters exist for the uptake of precursors (tryptophan, kynurenine). Peripheral XA passes the BBB and accumulates in several regions of the rat brain while endogenous natural XA is distributed at concentrations varying by region (0.1 up to 4–5 μM). BBB, blood–brain barrier; PFC, prefrontal cortex; XA, xanthurenic acid.



OAT3, which transport XA with K_m of about 4–6 μM in human oocytes (Uwai & Honjo, 2013). Administration via I.P. route of 50 mg/kg XA to Wistar rats demonstrates a significant increase in several brain regions of the treated animal, 30 min after injection. Among the brain structures investigated, accumulation of XA was very important (2- to 10-fold increase) in mesencephalic nuclei (A9–A10), amygdala, cortex, and striatum (caudate-putamen; Figure 3; Gobaille et al., 2008). This heterogeneity in XA accumulation probably reflects the density of transporters dedicated to the uptake of this compound).

The study of XA release from the prefrontal cortex (PFC) has been studied by microdialysis *in vivo*. Electrical stimulation or retro-dialysis of KCl or veratrine induces a 3- to 6-fold increase in the basal content of XA in the extracellular fluid. Blockade of voltage-dependent Na^+ by tetrodotoxin (TTX) or the absence of Ca^{2+} from the dialysis medium abolish totally the electrical-induced release. These results are in favor of an exocytotic type of release (Gobaille et al., 2008).

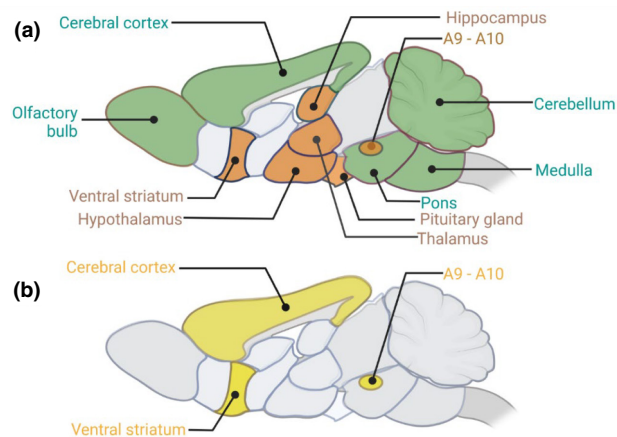
3.2 | XA binds to several GPCR's in brain and induces specific responses

To add further arguments to the hypothesis of the role of XA in intercellular brain signaling, we documented the existence of GPCRs that may be targets for XA in the CNS. A saturable and reversible binding for XA, distributed heterogeneously in the rat brain was first described (Taleb et al., 2012). This binding appears to be specific with regard to a large panel of known receptors. In addition, XA stimulates the binding of radioactive guanosine-5'-triphosphate (GTP) on synaptic membranes of rat brains indicating the participation of G proteins. Patch-clamp studies and experiments using Ca^{2+} imaging on NCB-20 cells that do not express calcium signals under the influence of glutamate, showed that XA activates cationic channels and increases intracellular Ca^{2+} concentrations.

In agreement with these data, a possible relationship between XA and modulation of group II glutamatergic metabotropic receptors by an agonist-like effect has been described (Fazio et al., 2015, 2017). Furthermore, XA inhibits the vesicular transport system of glutamate, which could explain the reduction in excitatory postsynaptic potential (EPSP) induced by XA observed in the gyrus dentate and the CA1 region of the hippocampus. The application of millimolar concentrations of XA in sections at the CA3 region of the hippocampus reduces the gamma-like oscillations (Herman et al., 2013) produced by the incubation of micromolar amounts of carbachol (Sathyaikumar et al., 2017). At least in these brain regions, the precursor of XA (3-HK) or XA itself reduces synaptic activity along with the release of glutamate. In addition, we showed recently that the local administration of low micromolar concentrations of XA via a cerebral dialysis probe significantly increases extracellular DA levels in the two regions tested in rats, specifically the frontal cortex and striatum (Taleb et al., 2021). This release was blocked by the NCS-486 antagonist of the XA receptor (Taleb et al., 2012). At the tissue level, the I.P. administration of XA to the animal also increases DA concentrations in several brain regions, including the two regions explored in microdialysis. In addition, chronic administration of XA *in situ* in the A10 and A9 nuclei in rats *in vivo* leads to a decrease in the discharge of these dopaminergic nuclei. In this domain, we have further explored the role of XA in the PFC.

3.3 | XA impact on PFC activity

Electrical stimulation of the ventral tegmental area (VTA) has been shown to induce a release of XA in the PFC (Gobaille et al., 2008). This electrical stimulation of the VTA also induces DA release in the PFC (Lohani et al., 2019). Thus, this TTX and Ca^{2+} -sensitive stimulated release of XA in the PFC can be interpreted as being either a release by the DA terminals, a release by DA-stimulated XA neurons



Physiological concentrations of XA in brain regions (Figure 3a)		Regions accumulating XA after IP administration (Figure 3b)
1 μM	0.1 – 0.4 μM	
Olfactory bulb Cerebellum Medulla Cortex Pons	Amygdala Globus pallidus Hippocampus Nuclei A9 A10 Hypothalamus Pituitary gland Septum Thalamus	Nuclei A9 A10 Amygdala Striatum Cortex

FIGURE 3 XA concentrations in rat brain. The measurements were carried out by HPLC and electrochemical detection. The animals were sacrificed by microwave irradiation which immediately blocks any further evolution of XA concentrations by metabolism and each region was quickly dissected and homogenized. Part A shows physiological levels of XA, which range from about 1 μM (green) to 0.1–0.4 μM (brown). Some regions do not have XA or have levels below 0.1 μM (not shown). Part B shows the brain regions accumulating the most XA after peripheral administration (I.P) of 50 mg/kg sodium XA-salt, 30 min after injection.

in the PFC, or both. Interestingly, XA immunoreactive cells in the PFC are juxtaposed to tyrosine hydroxylase (TH)-containing terminals (Roussel et al., 2016) suggesting a VTA DA neurons projections to XA neurons. This could represent an anatomical structure to a direct effect of DA neuron activities on the XA release observed in the PFC after VTA stimulation (Gobaille et al., 2008). XA localization in dendrites (Roussel et al., 2016) could lead to XA-stimulated release that determines the level of [XA] in the extracellular space of all regions where these dendrites are present. This could have a paracrine effect on cells expressing XA targets (Figure 4). According to the involved XA target, different effects can occur.

XA-specific receptor-mediated effect induces long-lasting membrane depolarizations (mins) through cation channel activation (Taleb et al., 2012) that could impact N-methyl-D-aspartate (NMDA) receptor activity by removing Mg²⁺ block and thus enhancing postsynaptic spiking activity which may contribute to an increase in PFC neurons ensemble activity and the power of gamma wave-form observed after VTA DA neuron stimulation. Since I.P. injected

and PFC local administration of XA enhanced extracellular DA in the PFC (Taleb et al., 2012), thus XA paracrine effect could have positive feedback on DA release in the PFC.

XA was also reported as an agonist of mGlu2/3 receptors (Fazio et al., 2015, 2017). In the PFC, mGluR3 is postsynaptically localized on basket cells and in some dendrites spin synapses (Arnsten et al., 2021; Datta & Arnsten, 2018). Its activation may increase mGluR3 agonists glutamate and NAAG (N-Acetyl-Aspartyl-Glutamate) release from basket cells. All these agonists, in a paracrine effect, would enhance mGluR3 activation and then inhibit the cAMP formation at postsynaptic spin synapses that will strengthen synaptic efficacy and cell firing (Arnsten et al., 2021). XA acting on presynaptic mGluR2, by inhibiting cAMP formation, would in contrast reduce excess of glutamate release, thus preventing excitotoxicity. Concurrently, XA can reduce the accumulation of glutamate in synaptic vesicles by competing at vesicular transporters VGLUTs. This effect could contribute to reducing the release of glutamate in the synaptic cleft and thus preventing excitotoxicity in a context where NMDA synapses are active by XA-induced long-lasting depolarizations. XA by acting through XA-specific and class II glutamate receptors would thus impact the activity in the PFC by permitting NMDA synapses activity and increasing synapse efficacy.

4 | THE BALANCE BETWEEN KYNA AND XA PARTICIPATES IN DA RELEASE REGULATION

4.1 | Opposing actions of KYNA and XA on DA activity of specific brain regions

In light of the new properties that have been described for XA in the brain, we propose a role for the KYNA/XA couple in the control of cerebral dopaminergic activity. Kynurenine and 3-HK are, respectively, the precursors of KYNA and XA and the balance of the synthesis between these two compounds depends mainly on the regulation of KMO activity. Inhibition of this enzymatic pathway has been shown to increase the concentration of KYNA but most probably also decrease the downstream metabolites, especially XA (Tufvesson-Alm et al., 2018). KYNA is essentially localized in astrocytes, while XA has a neuronal localization (Hubbard et al., 2015; Roussel et al., 2016). In addition, a significant portion of KMO activity has been described to be in neurons (Sathyaikumar et al., 2022). Therefore, a XA/KYNA compartmentalization exists, regulated in part by KMO activity, exercising opposite functions on the dopaminergic activity of some brain regions (Okuno et al., 2011; Rassoulpour et al., 2005; Tufvesson-Alm et al., 2018). Transgenic mice exhibiting a KMO K/O phenotype and a chronic increase in KYNA in brain showed an increase in the spontaneous activity of A10 dopaminergic neurons (Tufvesson-Alm et al., 2018). By contrast, repeated treatments with XA reduced the firing of the same nucleus, while the activity of the substantia nigra (SN, A9) remains unaffected (Taleb et al., 2021). The same opposition was observed concerning

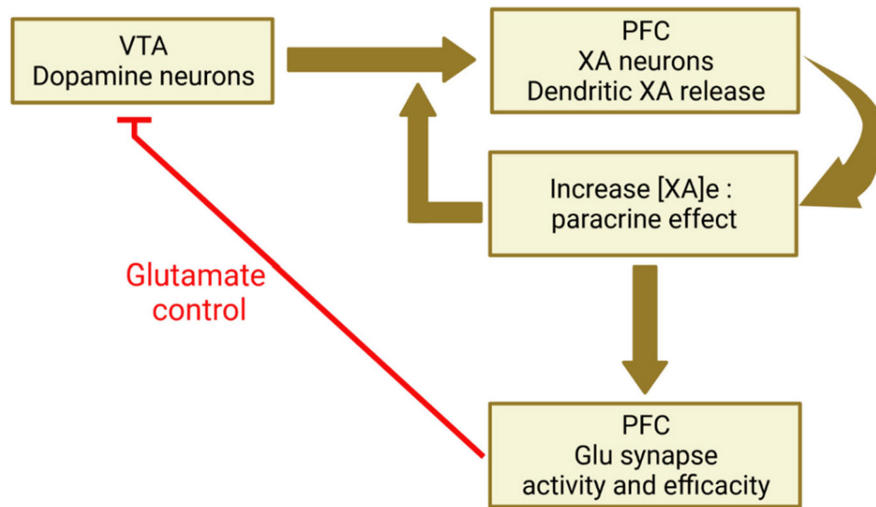


FIGURE 4 Diagram representing the impact of XA on the PFC activity following stimulation of VTA DA neurons. DA release in the PCF could increase XA release and extracellular XA concentration ([XA]e). XA paracrine effect on glutamatergic neurons through its XA-R could induce long-lasting depolarization (mins) that could relieve Mg²⁺ block of NMDA-R. These depolarizations may also increase neuronal firing and LFP oscillations. While through class II mGluRs, XA could increase synaptic efficacy and prevent excitotoxicity. Increased glutamatergic neuron activity involving class II mGluRs, could have negative feedback on VTA DA neuron activity. DA, dopamine; PFC, prefrontal cortex; VTA, ventral tegmental area; XA, xanthurenic acid.

the release of DA in the extracellular space measured by *in vivo* microdialysis. In both the PFC and the striatum, local administration of XA by retro-dialysis increases the release of DA, while peripheral injection via I.P. route was demonstrated to increase DA tissue contents. By contrast, local application of KYNA in the striatum reduces DA release (Erhardt et al., 2009). Our results showed the complete opposition of the effect between KYNA and XA regarding the accumulation and release of DA in brain regions, particularly the PFC.

The anatomical and functional proximity of XA-positive brain regions to dopaminergic brain areas raises the question of possible feedback control of XA on DA synthesis via the modulation of phenylalanine and tyrosine hydroxylase activities. Inhibition of tetrahydrobiopterin synthesis by nanomolar amounts of XA has been described, which is expected to affect the activity of several hydroxylases involved in the synthesis of neurotransmitters, including DA and serotonin, and a parallel increase in the KP (Haruki et al., 2016). The physiological role of these regulations remains unknown but may be important in some neuropsychiatric pathologies.

5 | XA IS AN ENDOGENOUS AND DIETARY COMPOUND FOR THE ACTIVATION OF ARYL HYDROCARBON RECEPTOR (AhR)

5.1 | Presumptive role in certain neurodegenerative mechanisms

AhR is a ligand-activated transcription factor, which was first identified as a mediator of dioxin toxicity activating the transcription of several drug-metabolizing enzymes like cytochrome P450 enzymes.

Once activated, the AhR of the cell cytoplasm translocates to the nucleus and binds to a specific DNA sequence to induce target gene transcription. The diet, microbiome, and metabolism of symbiotic organisms produce multiple AhR agonists that are involved in neoplastic and inflammatory processes affecting the CNS (Rothhammer & Quintana, 2019). The activity of catabolites of the tryptophan-kynurenine circuit produced by IDO1 is important for the proliferation and survival of the undifferentiated stage of human embryonic stem cells (Yamamoto et al., 2019). Tags: The role of kynurenine and its catabolites play a significant role in the regulation of mechanisms leading to neurodegeneration processes, in particular through the modulation of AhR (Cuartero et al., 2014, Garcia-Lara et al., 2015, Vecsei et al., 2013). Tags: Importantly, AhR is widely distributed in the body, especially in the gastrointestinal, cardiovascular systems, in the skin and participates in the regulation of the gut microbiota and the immune system. AhR mRNA is present in many nerve tissues, particularly in the cerebellum, cortex, and hippocampus. Its dysfunction involves circadian rhythm, heart muscle trophism, and BBB permeability (see for review (Kou & Dai, 2021, Mandal et al., 2023)). Besides xenobiotics, several endogenous and dietary compounds are AhR ligands generated by the metabolism of Trp and indole (Ma et al., 2020). Compared to the high-affinity ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), two compounds of the KP activate the human AhR in cell culture, in addition to cinnabarinic acid and 6-formylindolo-carbazole (FICZ): KYNA and XA were tested at 10 μM, the former being more potent than XA (Hubbard et al., 2015). However, while peripheral KYNA very poorly penetrates the BBB, XA administered peripherally or generated by the gut-brain axis is transported more easily and accumulates in specific brain regions. Similarly, the neuroactive hormone DA, which appears to be regulated by XA, has also been demonstrated to be an AhR active compound (Park et al., 2020).

Therefore, AhR could be activated in XA and DA neurons and interfere with the NF- κ B inflammatory transcription program (Figure 5), which could have a role in the prevention and propagation of cells death in neurodegenerative or autoimmune diseases of the CN (Grifka-Walk et al., 2021; Ojo & Tischkau, 2021; Wei et al., 2021). It was proposed that endogenous ligand of AhR, namely XA either produced by the gut microbiota (Sun et al., 2020) or administered peripherally, could have a beneficial effect on several physiological processes, including neuroprotection and preservation of glial cell functions during aging. This phenomenon could constitute a promising pharmacological approach, which can be extended to several CNS pathologies. Several recent studies have shown that the gut microbiota participates in the regulation of brain homeostasis through the relationship between the brain and the intestinal sphere (Ma et al., 2020). Because XA easily enters the CNS, it may be a primary

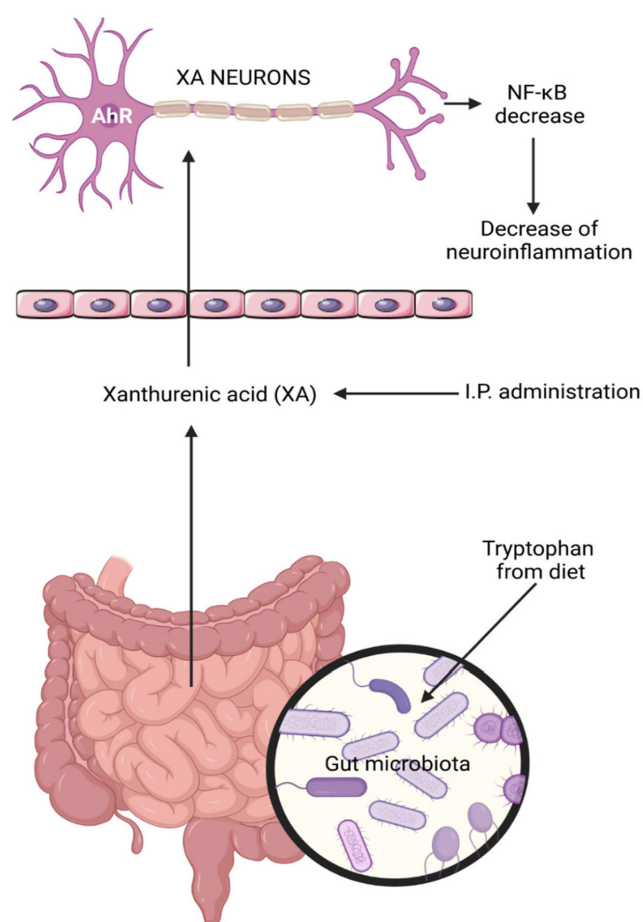


FIGURE 5 Among the functions of XA in the body is its activity as an endogenous ligand of AhR through the metabolism of tryptophan. As a result, diet, the activity of symbiotic microorganisms, enzymatic regulations leading to kynurenine and 3-HK modify XA levels, which leads to the activation of specific genes after translocation of the receptor in the nucleus. Peripheral administration of XA or structural analogs may be a method for modifying AhR activity and assessing its physiological role and participation in the mechanisms of certain CNS diseases. 3-HK, 3-hydroxykynurenine; AhR, aryl hydrocarbon receptor; CNS, central nervous system; I.P., intra-peritoneal; XA, xanthurenic acid.

compound among tryptophan metabolites to play a role in communication processes between the brain and the periphery of the body. Among the effects induced by AhR signaling, neurogenesis, autophagy but also cellular senescence have been invoked (Kondrikov et al., 2020; Wei et al., 2021; Wu et al., 2021). AhR could play an important role in certain neurodegenerative processes such as Alzheimer's disease by participating in the regulation of long-term neuroinflammatory processes. In some cancer models, the potentiation of XA production could be a deleterious effect on cell migration (Novikov et al., 2016). With this in mind, the role of XA in these processes could be modified by modeling active substances at the level of transport, metabolism, and recognition of XA by AhR and/or its specific membrane receptor. This opens up opportunities to test synthetic XA ligands in several neuropsychiatric diseases. It should be recalled that a specific GPCR/XA receptor antagonist has already been described and some of its interesting functions studied in cell culture and in vivo. (Taleb et al., 2012, 2021).

6 | A ROLE OF XA IN SCHIZOPHRENIA?

6.1 | XA could interfere with certain psychotic mechanisms

XA must be considered to have relevant functions as a Trp metabolite in some intercellular signaling in brain. Among these properties, several have been reported to be in relation to the specific interaction with GPCR's inducing in part a modification of some neurotransmitters like glutamate and DA.

XA has first been described as an agonist of mGlu2/3 receptors, directly or indirectly via an interaction with the vesicular glutamate transporter of brain synapses (Fazio et al., 2015, 2017). Considering that these metabotropic receptors have been implicated in the pathophysiology of schizophrenia and in the appearance of psychotic symptoms (Dogra & Conn, 2022; Long et al., 2022; Mazzitelli & Neugebauer, 2021; Stansley & Conn, 2018), XA was tested in animal models treated with MK-801 (i.e., dizocilpine is the most frequently used uncompetitive NMDA receptor antagonist in animal models to mimic psychosis for experimental purposes). Tested at 30–60 mg/kg, XA exhibits antipsychotic-like activity in mice, but not in mGLU2 $^{-/-}$ transgenic animals (Fazio et al., 2015). A decrease in XA concentrations in blood and cerebrospinal fluid (CSF) has been detected in schizophrenic patients compared to non-psychotic individuals (Curto et al., 2019). Reduced were also some metabolites of the KP downstream to KMO activity 3-HK, 3-HNA, quinolinic acid, indicating a permanent deficit at this level. Then, it could be predicted that the balance between KYNA/XA is most probably permanently modified with a simultaneous modification in the effect between inhibition/activation of glutamatergic global activities, either at the level of NMDA receptors (KYNA) or at the level of glutamate synapses functions (XA). Interestingly, an elevated concentration of KYNA has been described to induce psychotomimetic actions in

men while a decrease in XA is involved in a similar phenomenon in schizophrenic patients (Erhardt et al., 2007, 2017).

If we add to the opposite effects of the KYNA/XA couple on glutamatergic functionalities, the modifications induced by this same couple on the regulation of dopaminergic activity in certain strategic regions of the brain, we can wonder if these properties could have a role in the pathophysiology of schizophrenic disease as currently proposed (Buck et al., 2022; Howes et al., 2015). DA and glutamate are both believed to contribute fundamentally to mental dysfunctions characterized by positive or negative symptomatology in the expression of the disease. While the hypothesis of a KYNA role has long been suggested, the involvement of XA is a more recent possibility and a dysfunction in the balance between KYNA and XA levels has never been addressed to our knowledge (Figure 6).

Many pharmacological and preclinical studies involve both the glutamate and DA systems in the mechanisms of the disease. Risk factors, both genetic and environmental, involve the two systems that interact via many neural circuits. DA receptor antagonists of class D2 shave by far the most used pharmacological elements in most cases of schizophrenia (Wang et al., 2017), but it seems that glutamatergic dysfunctions also possess a role, perhaps anticipating dopaminergic abnormalities. In this context, a role of XA and the KYNA/XA couple can be a significant element. In addition, an imbalance of this pair of substances has been detected in the serum of a large population of schizophrenic patients, this phenomenon can participate in the production of symptomatology. Compartmentalization of changes in serum XA levels versus plasma levels has been identified as a potential marker of schizophrenic pathology, without specificity with patient sex or comorbidities such

as insulin resistance or obesity (Oxenkrug et al., 2019). An important step for the study and confirmation of these results could be the use of XA receptor agonists or antagonists in various animal models similar to human disease (Bialon & Wasik, 2022; Gonzalez-Rodriguez et al., 2023).

7 | XA INVOLVEMENT HAS BEEN POSTULATED IN OTHER PATHOLOGIES

The participation of XA in various pathologies has been invoked and may a priori be either interaction with AhR, or with glutamate receptors or transporters, or with its specific membrane receptor. It is therefore difficult to dissect the role of each target or even to the combination of interactions with these various sites in the results described in various studies. In most cases, alterations in blood XA concentrations or CSF have been demonstrated not in isolation, but in the context of evidence of a modification of several intermediates of the kynurenine cycle, in relation to each other. Inflammatory or nutritional factors have likely effects on several intermediates of the cycle, the inhibition of KMO described as beneficial in degenerative processes alters KYNA, but also 3-HK and its metabolite XA, as well as probably many compounds synthesized downstream. KAT's inhibitors interact not only on KYNA metabolism but their probable influence on XA levels is generally ignored, although they may be concerned theoretically (Shen et al., 2023). In other areas, the action of XA has been described both at the level of the ocular lens (Roberts et al., 2001) but also has a role in limiting the mobility of tumor

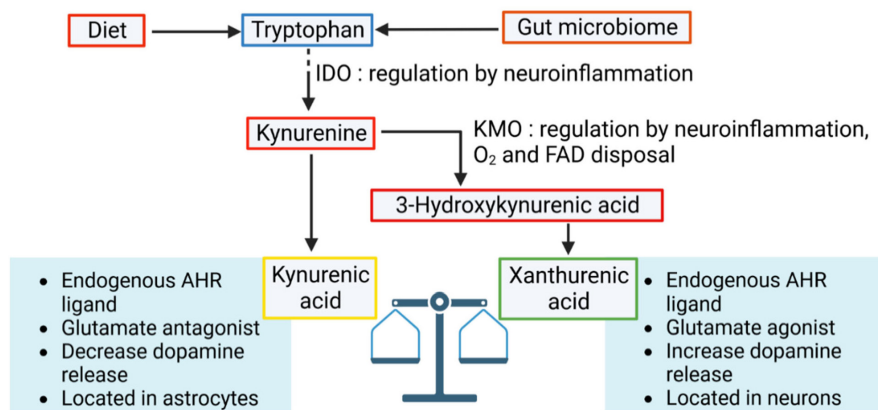


FIGURE 6 The kynurenine cycle, which originates from the essential amino acid tryptophan, is composed of multiple substances with different implications in neuroprotection, neuroexcitation, neurodegeneration, and neuroinflammation. The various compounds of this cycle are not independent of each other because they are subject to several regulations involving the entire cycle, altered under certain pathological conditions. An example of this interdependence is schematized on this figure, where the couple of related compounds KYNA/XA have certain opposite functions that can account for their possible simultaneous alterations in psychotic pathologies such as schizophrenia. From kynurenine, KYNA or XA synthesis are both mediated by vitamin B6-dependent kynurenine aminotransferases (KCAT's). Importantly, the production of XA goes through the synthesis of 3-HK dependent on the activity of KMO, which regulates the concentrations of 3-HK and XA. Inhibition of KMO induces an increase in KYNA (neuroprotective for its anti-glutamatergic functions) and a decrease in 3-HK (neurotoxic?) and XA. In a general field, a lot of work has been devoted to KYNA while the interest of XA was considered as a route to eliminate 3-HK mainly. 3-HK, 3-hydroxykynurenine; KMO, kynurenine monooxygenase; KYNA, kynurenic acid; XA, xanthurenic acid.

cells in glioblastomas in vitro (Varricchio et al., 2023). More generally, the kynurenine cycle and several of its intermediates have been implicated in the pathophysiology of several neuropsychiatric disorders (Davidson et al., 2022; Muneer, 2020). The bioavailability of tryptophan plays a role in many neural mechanisms and in the regulation of immune processes (Tanaka et al., 2021), in addition to the fact that this amino acid is the precursor to serotonin, melatonin, and tryptamine and is the basis for the genesis of nicotinamide dinucleotide (NAD). The serotonergic system plays an important role in mood regulation mechanisms and in depressive illness. In bipolar disorder, activation of several intermediates of the kynurenine cycle has been reported (Trepici et al., 2021), fueling interest in its in-depth study, the regulation of its enzymatic steps, and the mutual interrelationships between the various metabolites that constitute it.

8 | CONCLUSIONS AND FUTURE PERSPECTIVES

Considered until recently as a metabolite of the kynurenic cycle without a proven functional role, results described so far argue in favor of a role for XA in brain signaling, largely in symbiosis with its peripheral compartments (diet, gastrointestinal, and hepatic metabolism) since it penetrates easily several brain structures. There is a neuronal accumulation and release of XA inducing an electrophysiological response that appears to be mediated by a specific GPCR that can be activated by peripheral XA or inhibited by a synthetic inhibitor, paving the way for therapeutic perspectives. This is reinforced by the fact that XA modulates prefrontal dopaminergic influences and interferes with glutamatergic innervation. Its role in the mechanism of certain psychotic phenomena has been proposed. More generally, the functions of XA must be considered in direct relation to its structural partner. Indeed, KYNA has several functions opposite to XA.

Several metabolites downstream of KMO are known to be excitotoxic, stimulating glutamatergic activity, and whose levels are expected to be decreased by the drop in 3-HK synthesis. Among these compounds is XA. This is not independent of KYNA and the entire homeostasis of the kynurenine ring is probably reworked by the modification of the KMO activity or by the influence of trophic or inflammatory factors. As a result, the respective responsibilities of the two KYNA/XA metabolites in various neurological diseases (epilepsy, depression, neurodegeneration) seem to require a reexamination from a global perspective.

AUTHOR CONTRIBUTIONS

Christian Klein: Visualization; writing – review and editing. **Ayikoe-Guy Mensah-Nyagan:** Validation; writing – review and editing. **Hélène Jeltsch-David:** Validation; writing – review and editing. **Michel Maitre:** Conceptualization; validation; writing – original draft; writing – review and editing. **Omar Taleb:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest between the authors of this manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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ORCID

Michel Maitre  <https://orcid.org/0000-0003-1478-4806>

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