The Kynurenine Pathway at the Interface Between Neuroinflammation, Oxidative Stress, and Neurochemical Disturbances: Emphasis in Schizophrenia

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Abbreviations

3-HANA	3-hydroxyanthranilic acid
3-HAO	3-hydroxyanthranilic acid 3, 4-dioxygenase
3-HK	3-hydroxykynurenine
ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
BBB	Blood brain barrier
CNS	Central nervous system
DA	Dopamine
GABA	Gamma-aminobutyric acid
Glu	Glutamate

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H_2O_2	Hydrogen peroxide
HO-1	Heme oxygenase-1
IDO	Indoleamine 2,3-dioxygenase
KATs	Kynurenine aminotransferases
KMO	Kynurenine 3-monooxygenase
KP	Kynurenine pathway
KYN	Kynurenine
KYNA	Kynurenic acid
LDL	Low-density lipoprotein
MAPKs	Mitogen-activated protein kinases
NF-κB	Factor nuclear factor-kappa B
NOS	Nitric oxide synthase
PFC	Prefrontal cortex
QUIN	Quinolinic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SP	Schizophrenia
TDO	Tryptophan 2,3-dioxygenase
Trp	Tryptophan
XA	Xanthurenic acid
α7nAChR	α7 nicotine acetylcholine receptor

1 Oxidative Stress and Inflammation in the Brain

Free radical formation is part of the physiological processes of aerobic metabolism. In this manner, cellular metabolism produces free radicals under physiological conditions that are involved in critical functions during neuronal development, differentiation, and signal transduction (Garthwaite et al. 1988; Matsumoto et al. 1993). Oxidative stress is a cytotoxic condition taking place in different tissues when antioxidant mechanisms are overwhelmed by reactive oxygen species (ROS) (Halliwell 2006). Thus, oxidative stress is a threshold phenomenon characterized by a major increase in the amount of oxidized cellular components. Overproduction of ROS results in oxidative damage, including lipid peroxidation, protein oxidation, and DNA damage, which can lead to cell death (Floyd 1999; Love 1999; Phillis 1994). Furthermore, ROS can activate diverse downstream signaling pathways, such as mitogen-activated protein kinases (MAPKs) or the transcription factor nuclear factor-kappa B (NF-κB). Actually, the role of ROS in inflammatory modulation involves NF-κB, since this factor becomes more transcriptionally active in response to the degradation of IκB by ROS, IκB being the inhibitory partner of nuclear factor κB that sequesters it in the cytosolic domain (Hayden and Ghosh 2004), thereby regulating the expression of genes encoding for a variety of proinflammatory proteins. The consequences of excessive inflammatory responses comprise secretion of high levels of proinflammatory cytokines and chemokines and production of more free radicals

causing oxidative stress, which cannot only damage neurons through the downregulation of neurotrophins and their receptors but also by blocking neurogenesis.

Moreover, the brain is particularly susceptible to the damage caused by oxidative stress, due to the high rate of oxidative metabolic activity to support its normal functions, high polyunsaturated fatty acid contents, relatively low antioxidant capacity, and inadequate neuronal cell repair activity (Traystman et al. 1991). Indeed, intracellular oxidative stress is highly associated with the development of neurodegenerative diseases and brain aging (Emerit et al. 2012; Cui et al. 2012), suggesting that the CNS is an important target for oxidative stress. Inflammatory processes could favor proinflammatory molecules from the periphery to invade the CNS, increasing cytokines, and activating glial cells to produce an amplified response. Thus, factors like cytokines, cyclooxygenases, and prostaglandins may act as extracellular signals to generate additional ROS that are associated with decreased neuronal function or glial/neuronal interactions (Rosenman et al. 1995; Schipper 1996; Steffen et al. 1996; Stella et al. 1997; Woodroofe 1995). In this context, metabolites from the kynurenine pathway are implicated in different neurodegenerative disorders because they can be modulated by both proinflammatory cytokines and free radicals.

2 Kynurenine Pathway (KP)

The kynurenine pathway (KP) represents a major route for the catabolism of tryptophan (Trp) in mammals. The human body is unable to synthesize Trp; for this reason, this amino acid is obtained from external sources (Chen and Guillemin 2009). Trp can only be transported across the blood–brain barrier (BBB) in its free form by the competitive and nonspecific L-type amino acid transporter (Hargreaves and Pardridge 1988). The result of KP is to use Trp to produce the essential pyridine nucleotide end product, NAD^+ (Magni et al. 1999), which plays a key role in several biochemical and biological processes (Fig. 1).

In the first step of this metabolic process, Trp is oxidized by cleavage of the indole ring by two dioxygenases: indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), to further produce N-formylkynurenine. TDO was long thought to be exclusively localized in the liver, but now is known to be also expressed in the brain (Haber et al. 1993) and can be induced by corticosteroids (Salter and Pogson 1985). In turn IDO is present in two isoforms (Ball et al. 2009), it predominates extrahepatically and can be expressed in various cell types throughout the body, including fibroblasts, dendritic cells, monocytes, macrophages, and microglia. IDO can be induced by a number of cytokines such as IFN-α and TNF-α (Guillemin et al. 2001, 2005; Robinson et al. 2005). This enzyme is a major immunomodulator, showing increased activity and expression in the brain in association with macrophage infiltration and microglial activation (Saito et al. 1993). Of note, interferon gamma (IFN-γ) is able to induce both gene expression and enzymatic activity of IDO-1 (Dai and Gupta 1990; Hassanain et al. 1993; Babcock and Carlin 2000). IDO is also unique in regard to its known property of using superoxide anion

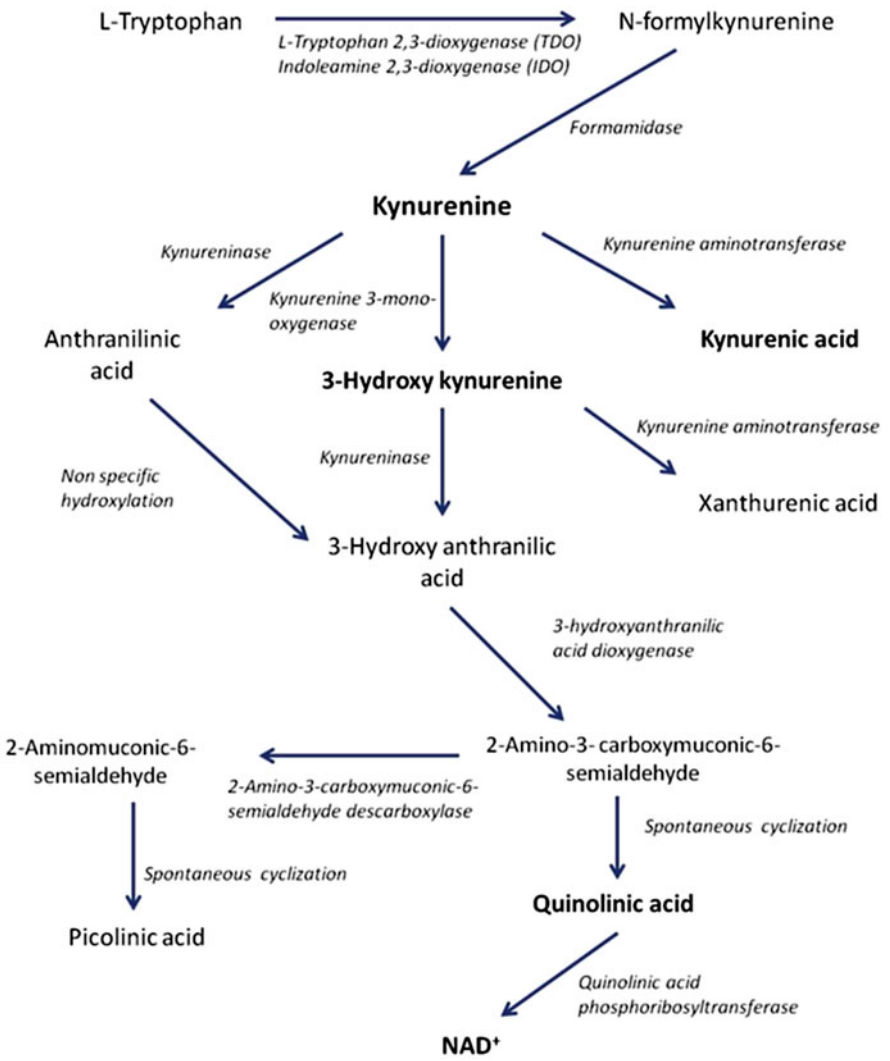

Fig. 1 Schematic representation of the tryptophan metabolism pathway known as kynurenine pathway

radical as substrate and cofactor (Thomas and Stocker 1999), thus requiring the presence of radical generating systems such as ascorbate and xanthine-xanthine oxidase. In addition, the enzyme is known to be inhibited both by superoxide dismutase (SOD) (Hirata and Hayaishi 1971) and nitric oxide (Thomas et al. 1994).

The Trp catabolite N-formylkynurenine is then hydrolyzed to form the first stable metabolite kynurenine (KYN) by the action of kynurenine formamidase. In the brain, KYN gives rise to two physically segregated branches of the pathway, producing 3-hydroxykynurenine (3-HK) and its corresponding downstream metabolites 3-hydroxyanthranilic acid (3-HANA) and quinolinic acid (QUIN) in microglial

cells, as well as kynurenic acid (KYNA) in astrocytes. Thus, KYN is metabolized by three enzymes: (1) kynurenine 3-monooxygenase (KMO), a flavin-containing monooxygenase requiring the presence of NADPH as an electron donor (Charconnet-Harding et al. 1953; Stevens and Henderson 1959) to catalyze the hydroxylation of KYN to 3-HK; (2) kynurenine aminotrasferases (KATs), which catalyze the transamination of KYN to KYNA—although several of these enzymes may participate in cerebral KYNA biosynthesis under physiological and physiopathological conditions, it appears that the pool of KYNA that can be most readily mobilized in the brain is largely provided by KAT II (Amori et al. 2009); and (3) kynureninase, which catalyzes the degradation of KYN to anthranilic acid (AA).

Mammalian kynureninase is a pyridoxal phosphate-dependent enzyme that preferentially recognizes 3-HK over kynurenine, catalyzing the formation of 3-HANA (Kawai et al. 1988). Of note, AA is a better precursor for 3-HANA within the brain than 3-HK (Baran and Schwarcz 1990). KAT II—and possibly other KATs—converts 3-HK into xanthurenic acid (XA). 3-HANA is the substrate for 3-hydroxyanthranilic acid 3,4-dioxygenase (3-HAO), which is present with relative abundance in the brain and is known to be inhibited by several metals ions (Foster et al. 1986), thereby forming 2-amino-3-carboxymuconic-6-semialdehyde. Under physiological conditions, 2-amino-3-carboxymuconic-6-semialdehyde spontaneously rearranges to form QUIN. Notably, the brain seems to contain very little 2-amino-3-carboxymuconic-6-semialdehyde decarboxylase, an enzyme that deflects the metabolic cascade towards the production of picolinic acid (PIC) (Pucci et al. 2007). The cerebral activity of the QUIN's degradative enzyme, quinolinate phosphoribosyltransferase, is very low (Foster and Schwarcz 1985), making this enzyme one of the gatekeepers for the synthesis of NAD^+.

Excessive formation of 3-HK, QUIN, and/or KYNA could play a significant role in brain pathology since these metabolites have been shown to exhibit either neurotoxic or neuroprotective properties, as well as antioxidant or pro-oxidant effects. Therefore, metabolites have been implicated in different neurologic and psychiatric disorders (Moroni 1999; Müller and Schwarz 2007; Németh et al. 2006; Oxenkrug 2011; Ruddick et al. 2006; Schwarcz and Pellicciari 2002).

3 KP Metabolites with Pro- and Antioxidant Properties Can Modulate Oxidative Stress

The CNS plays a key role in the maintenance of homeostasis and physiological functions in mammals. However, its biochemical and cytological characteristics make it vulnerable to the action of different cytotoxic agents. Among the mechanisms leading to neurodegeneration and cell death, ROS-induced oxidative stress plays a pivotal role. Oxidative stress occurs when cellular antioxidant defense mechanisms fail to counterbalance and control endogenous ROS and reactive nitrogen species (RNS) generated either from normal oxidative metabolism or from pro-oxidant conditions (Kohen and Nyska 2002; Berg et al. 2004). ROS/RNS are also

Table 1 Metabolites from KP with pro-oxidative and scavenger properties

Metabolite	Species produced	Species scavenged
Trp		H_2O_2
KYN		$OH^{\bullet}$, $ONOO^{-}$, H_2O_2
3-HK	H_2O_2	$OH^{\bullet}$, NO
3-HANA	$O_2^{\bullet-}$, H_2O_2	$ROO^{\bullet}$, NO
QUIN	$OH^{\bullet}$, $ONOO^{-}$	
XA		$ROO^{\bullet}$, $O_2^{\bullet-}$, $OH^{\bullet}$
AA		H_2O_2
KYNA		$O_2^{\bullet-}$, $OH^{\bullet}$, $ONOO^{-}$

known to modulate inflammation. There is a close relation between oxidative stress and the pathogenesis of neurodegenerative diseases. In this context, KP generates metabolites exhibiting antioxidant and pro-oxidant properties (Table 1), which production can be modulated by the prevailing redox status in cells; the imbalance in these metabolites is implicated in different pathologies of the CNS.

Under physiological conditions, KP modulates glucose metabolism: while ATP and 3-HANA formed from this pathway activate glycolysis—through which glycogen is stored in the cells to be used in case of energy stress or glucose depletion—QUIN inhibits gluconeogenesis (Lardy 1971). Several KP metabolites participate in complex pro- and antioxidative processes in the brain (Giles et al. 2003). In particular, 3-HK and 3-HANA readily autooxidize under physiological conditions, producing in the process hydrogen peroxide (H_2O_2) and highly reactive hydroxyl radicals (Goldstein et al. 2000). However, these effects are currently balanced by the antioxidant capacity of KYNA and XA due they can scavenging radicals (Lugo-Huitrón et al. 2011a; Christen et al. 1990).

3-HK is present in the brain of mammals at nanomolar concentrations (Pearson and Reynolds 1992). This metabolite undergoes autooxidation and can be converted into quinonimines with the accompanying generation of ROS (Hiraku et al. 1995). The ability of 3-HK to generate ROS seems to be the mechanism by which it causes neurotoxicity, given that cell damage induced by this metabolite is prevented by coadministration of metal chelating agents and free radical scavengers (Chiarugi et al. 2001; Eastman and Guilarte 1990; Goldstein et al. 2000; Nakagami et al. 1996; Okuda et al. 1996). 3-HK uptake into cells is required for neurotoxicity, as its inhibition by competing large neutral amino acids prevents this damage. In addition, 3-HK toxicity depends on the cellular type because cortical and striatal cells were more vulnerable to cerebellar neurons (Okuda et al. 1998). The levels of 3-HK are increased in the brains of mice following immune activation or administration of interferon-γ (Saito et al. 1992). It is likely that some of the deleterious actions attributed to 3-HK are actually due to its metabolite 3-HANA, since the later readily undergoes autooxidation with the formation of superoxide anions (Dykens et al. 1987, 1989). Toxic pro-oxidant effects of 3-HK and 3-HANA were mainly observed in neuronal cell cultures exposed for long periods and high concentrations (100–200 mM) of these compounds (Lee et al. 2001, 2004). Furthermore, 3-HK potentiates QUIN toxicity; intrastriatal co-injection of these agents in low doses, which

alone cause only minimal or no neurodegeneration, results in substantial neuronal loss (Guidetti and Schwarcz 2003). Nevertheless, antioxidants such as N-acetylcysteine can attenuate the damage produced by 3-HK in vivo, whereas catalase and glutathione can prevent the toxicity evoked by this metabolite in neural hybrid cell line N18-RE-105. Our group has recently collected experimental evidence showing that 3-HK can also act as a peroxynitrite scavenger, partially preventing ROS formation in rat brain homogenates exposed to $FeSO_4$ (unpublished data). This evidence is in agreement with previous reports describing 3-HANA and 3-HK as potent radical scavengers since they can protect B-phycoerythrin from peroxyl radical-mediated oxidation for longer periods of time at equimolar concentrations of ascorbic acid and a water-soluble analogue of vitamin E (Christen et al. 1990). These two metabolites also inhibited spontaneous lipid peroxidation in the brain, protecting cerebral cortex against oxidative damage even in the presence of Fe III or Fe II, which stimulate auto-oxidation of these metabolites and hydroxyl radical formation, respectively. 3-HK is also able to scavenge hydroxyl radicals because it reduces 2-deoxy-D-ribose oxidation (Leipnitz et al. 2007). Hence, it is conceivable that under conditions in which 3-HK acts as antioxidant, the autooxidation or hydroxyl formation did not occur or was insufficient to overcome the antioxidant properties of this metabolite.

3-HANA has also been shown to generate hydrogen peroxide and superoxide in the presence of transition metal ions such as copper (Goldstein et al. 2000). However, 3-HANA can also act as an antioxidant, scavenging peroxyl radicals more effectively than equimolar concentrations of either ascorbic acid or Trolox (Christen et al. 1990). 3-HANA was highly effective in inducing in astrocytes the expression of heme oxygenase-1 (HO-1), an antioxidant enzyme with anti-inflammatory and cytoprotective properties in human glial cells (Krause et al. 2011). Additionally, 3-HK and 3-HANA are also efficient NO scavengers (Backhaus et al. 2008), and 3-HANA also prevented the spontaneous oxidation of GSH (Leipnitz et al. 2007). It has been observed that 3-HANA acts as a co-antioxidant for the low-density lipoprotein (LDL), preventing lipid peroxidation. It was then postulated that 3-HANA regenerates α-tocopherol, which is the endogenous antioxidant for LDL, by reducing the α-tocopheroxyl radical (Christen et al. 1994; Thomas et al. 1996).

On the other hand, the toxic actions of QUIN are primarily linked to N-methyl-D-aspartate receptor (NMDAr) overactivation through excitotoxic events (Stone 1993; Susel et al. 1989). More recently, evidence involving oxidative stress as an integral part of the toxic model induced by QUIN has appeared (Rodríguez-Martínez et al. 2000; Behan et al. 1999). Some studies suggest that QUIN stimulates lipid peroxidation in brain tissue (Ríos and Santamaría 1991), and this effect is likely to be mostly dependent on NMDAr overactivation since this marker of oxidative stress is attenuated by NMDAr antagonists like KYNA and MK-801 (Santamaría and Ríos 1993). QUIN has also shown to induce peroxynitrite formation through a concerted inhibition of SOD activity and increased activity of nitric oxide synthase (NOS) (Pérez-de la Cruz et al. 2005). Noteworthy, it seems that only a small fraction of this damage corresponds to an NMDAr-independent component (Santamaría et al. 2011a; Behan et al. 1999; Stone et al. 2000), and this is probably due to

the ability of this metabolite to form complexes with iron (II) (Stipek et al. 1997). Once these complexes are autooxidized, they yield hydroxyl radical formation through the Fenton reaction (Pláteník et al. 2001; Santamaría et al. 2011b). Therefore, QUIN is a prototypical molecule combining excitotoxic and pro-oxidant properties.

XA has been shown to act as a peroxyl radical scavenger in vitro, but its function as an antioxidant in vivo has been considered unlikely because the concentrations that were found in the tissue that has been studied (mouse lung) were in the low micromolar range (Christen et al. 1990). In the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) system, XA scavenged superoxide anions (Zsizsik and Hardeland 1999a). A recent study evaluated the antioxidant action of XA using heme and iron as promoters of radical formation: in this model, XA proved to be a powerful antioxidant, inhibiting lipid peroxidation induced both by heme and iron in a pH-dependent manner (Lima et al. 2012).

In regard to KYNA, some studies have shown that this metabolite scavenges hydroxyl radicals, efficiently protecting 2-deoxyribose when hydroxyl radicals were generated photolytically from N-hydroxy-2-pyridinethione (Zsizsik and Hardeland 1999b, 2001). KYNA also prevented the ROS production and lipid peroxidation induced by $FeSO_4$ and 3-nitropropionic acid in rat brain homogenates and decreased the hydroxyl radical production in vivo, independently of its activity on NMDAr and nicotinic receptors (Lugo-Huitrón et al. 2011a). We have collected recent evidence demonstrating that KYN, the direct precursor of KYNA, exerts stronger scavenger properties since it was able to scavenge hydroxyl radicals and peroxynitrite in synthetic medium and reduced ROS formation in rat brain homogenates exposed to $FeSO_4$ and peroxynitrite (Ugalde-Muñiz et al. 2012). Additionally, upon controlled conditions, peroxynitrite is capable of promoting KYNA production using L- and D-KYN as substrates (Lugo-Huitrón et al. 2011b). These data correlated with the study conducted by Zsizsik and Hardeland (2001) in which the incubation of KYN with H_2O_2 yields KYNA formation, a reaction that was enhanced in the presence of peroxidase. However, KYNA strongly potentiated the pro-oxidant behavior of δ-aminolevulinic acid, generating the degradation of 2-deoxyribose (Coto-Montes et al. 2001). Altogether, this evidence suggests that metabolites of KP exert both antioxidant and pro-oxidant properties, depending on the prevailing redox status.

4 Inflammation

Psychiatric disorders are associated with mild proinflammatory events. There is evidence demonstrating that KP is upregulated in inflammatory states, with activated macrophages and microglial cells producing QUIN together with other cytotoxins (Espey et al. 1997; Myint 2012). During inflammatory processes, the increased degradation of Trp and the peripheral amounts of KYN are propitious for KP metabolism in the brain, given that KYN can be transported through the BBB. Also, during inflammatory processes, KYN metabolism is increased. Most of KP metabolites contribute to homeostasis in the brain through their modulatory actions on neurotransmitters and redox status. Up to date, the unbalance in KP metabolites has

been implicated in a variety of disorders of the CNS, including the AIDS-dementia complex, Alzheimer's disease, schizophrenia, Huntington's disease, amyotrophic lateral sclerosis, etc. (Guillemin et al. 2005; Beal et al. 1990). Furthermore, during the occurrence of neuroinflammatory processes, when KP is activated in microglial cells and/or when invading macrophages infiltrate the brain, the concentrations of kynurenines may increase dramatically, reaching the micromolar range within the brain. In this regard, it is known that IFN-α can induce IDO, KMO, and 3-HAO. When IDO is induced by IFN-α, it yields a substantial increase in KYNA concentrations and other tryptophan metabolites.

The inflammatory cytokines IL-1 and TNF-α, and lipopolysaccharide (LPS), act synergistically with IFN-α to induce IDO (Robinson et al. 2005; O'Connor et al. 2009). Human microglia, blood macrophages, and mixed cultures of human fetal brain cells can ordinarily convert tryptophan, kynurenine, or 3-HK into QUIN even if there is no immune stimulation (Heyes et al. 1992). Human macrophages stimulated with TNF-α or IFN-γ yielded large amounts of QUIN (Pemberton et al. 1997). Kappa opioid receptors modulate the release of QUIN from microglial cells in culture (Chao et al. 2000). Interestingly, the amount of QUIN in the brain after immune stimulation can be prevented either by inhibitors of Trp metabolism or by compounds able to suppress the activation of immune-competent cells (Saito et al. 1994). 3-HANA and QUIN induce selective apoptosis of HT1 cell through the activation of caspase-8 and the release of cytochrome c from mitochondria (Fallarino et al. 2002) as well as by mean of processes mediated by oxygen-derived free radicals (Grohmann et al. 2003). Additionally, QUIN has been shown to induce the expression of chemokines and chemokine receptors in astrocytes, thereby leading to a possible amplification of brain inflammation (Guillemin et al. 2003). The synaptic and neuronal damage initiated by the QUIN-induced activation of microglia eventually leads to apoptotic cell death of oligodendrocytes and microglia, together with a loss of GFAP positive astrocytes (Dihné et al. 2001).

Loss of 3-HANA may have important consequences for the immune system. 3-HANA inhibits the proliferation of $CD8^{+}$T cells (Weber et al. 2006). It can also suppress the responses of T cells to allogeneic stimuli (Terness et al. 2002), acting primarily on Th1 rather than Th2 cells (Fallarino et al. 2002). At molecular level, it has been demonstrated that 3-HANA can suppress the activation of the proinflammatory transcription factor NFκB (Hayashi et al. 2007; Sekkaï et al. 1997) as well as inhibiting nitric oxide synthase (Sekkaï et al. 1997; Oh et al. 2004). This evidence suggests that 3-HANA seems to be protective, limiting the inflammatory response—including the activation of microglia, which is thought to contribute to brain damage following stroke. In addition, AA interacts with copper to form an anti-inflammatory complex able to remove highly injurious ROS (Miche et al. 1997; Halova-Lajoie et al. 2006).

It has been shown that inflammation plays a key role in the pathological onset of depression, and since cell-mediated immune activation induces IDO, this effect would lead to an increase in the Trp metabolism, reducing its levels in plasma, increasing the formation of KP metabolites, and decreasing serotonin synthesis. Altogether, these effects could explain the lower levels of this neurotransmitter and hypoactivation of its receptors observed in pathological conditions (Maes and Meltzer 1995). Additionally, generation of oxidative and nitrosative stress is an important mechanism

contributing to toxicity in inflammation and depression (Maes and Meltzer 1995; Maes et al. 2011), and because IDO employs superoxide anion as oxidant factor (Sun 1989), its activity could be even more augmented.

Recently, KYNA was identified as a ligand of GPR35 (Wang et al. 2006). Among immune cells, GPR35 is highly expressed in human $CD14^+$ monocytes, T cells, neutrophils, and dendritic cells, with lower expression levels in B cells, eosinophils, basophils, and iNKT cells; in the nervous system, it is mainly expressed in the dorsal root ganglia (Wang et al. 2006; Fallarini et al. 2010). The discovery that KYNA is an endogenous ligand for GPR35 further highlighted the importance of KP in regulating immune functions since the activation of GPR35 inhibits TNF-α release by macrophages under inflammatory conditions induced by LPS; in this context, KYNA might exert an anti-inflammatory effect (Wang et al. 2006). Additionally, GPR35 decreases intracellular Ca^{2+} probably by inhibiting its entrance (Oshiro et al. 2008); therefore, KYNA probably exerts an effect on the release of inflammatory mediators and excitatory amino acids from glial cells. Nevertheless, this action still remains unclear since KYNA activates the receptor at relatively high concentrations (10–100 μM), and so, it does not exert influence on extracellular neurotransmitters levels (Moroni et al. 2012).

The ligand-activated transcription factor aryl hydrocarbon (AHR) is also activated by KYNA. Considered as a xenobiotic receptor, AHR regulates the expression of different inflammatory intermediates and can facilitate carcinogenesis (DiNatale et al. 2010; Moroni et al. 2012). However, KYNA is not the only metabolite from KP that activates this receptor as kynurenine has been shown to act as agonist on AHR; actually, kynurenine seems to be more active than KYNA in this effect (Nguyen et al. 2010; Optiz et al. 2011), and it has been hypothesized that AHR can be activated by other KP metabolites, which in turn means a contribution of KP to the immunosuppressant action of T cells in carcinogenic processes (Mezrich et al. 2010; Moroni et al. 2012).

Another KP metabolite, PIC, is an unselective metal ion chelator (Aggett et al. 1989) that activates macrophages via induction of macrophage inhibitory proteins MIP-1α and MIP-1β (Bosco et al. 2000). Its effect is potentiated by simultaneous IFN-α treatment (Pais and Appelberg 2000). It possesses both extracellular and intramacrophage antimicrobial activity (Abe et al. 2004).

5 Neurochemical Modulation by KYNA

Inflammatory reactions and enhanced oxidative stress are recognized as two important factors associated with KP under both physiologic and pathologic conditions. Importantly, the imbalance in KP metabolites formation has a direct effect on neurotransmission, as they can modulate the release of glutamate (Glu), dopamine (DA), gamma-aminobutyric acid (GABA), and acetylcholine.

The major KP metabolite considered as a neuronal inhibitor is KYNA, which is synthesized and released by astrocytes and antagonizes NMDAr (Kessler et al. 1989)

and α7 nicotine acetylcholine receptor (α7nAChR) (Hilmas et al. 2001). As previously described, KYNA synthesis is mediated by KATs. Four KAT isoforms have been described so far (KAT I–IV), from which KAT I and KAT II are the most studied.

Activation of α7nAChR facilitates the release of multiple neurotransmitters, thereby providing multiple opportunities for modulation of synaptic communication. Stimulation of presynaptic α7 receptors directly facilitates Glu and GABA release (Wonnacott et al. 2006; Dani and Bertrand 2007). Indeed, DA, norepinephrine, and serotonin are indirectly modulated by α7 receptor-induced facilitation of Glu and GABA release in various brain regions (Kaiser and Wonnacott 2000; Wonnacott et al. 2006; Dani and Bertrand 2007; Sher et al. 2004; Gotti et al. 2006). At a functional level, enhanced KYNA in the brain has been demonstrated to cause cognitive deficits in animals (Shepard et al. 2003; Erhardt et al. 2004; Chess et al. 2009). Interestingly, reductions in brain KYNA levels cause significant cognitive improvements, which can be demonstrated both in behavioral paradigms and using electrophysiological outcome measures (Potter et al. 2010). Decreased KYNA levels lead to enhanced extracellular concentrations of Glu and acetylcholine, indicating that endogenous KYNA might function as a bidirectional modulator of glutamatergic and cholinergic neurotransmissions (Konradsson-Geuken et al. 2010; Wu et al. 2010; Zmarowski et al. 2009).

The fact that KYNA can directly influence neurotransmission is quite relevant as this metabolite can influence neuronal excitability but is limited to cross the BBB and can enter the brain only under certain circumstances. The ability of KYNA to enter the CNS can be augmented when the BBB is compromised. Modest elevations or reductions in KYNA levels reduce or facilitate extracellular DA and Glu release, respectively (Rassoulpour et al. 2005; Kaiser and Wonnacott 2000; Wu et al. 2007; Carpenedo et al. 2001; Alkondon et al. 2004). Accordingly, dysregulation of endogenous KYNA may contribute to the physiopathology of several neuropsychiatric disorders, including schizophrenia (SP). Elevated KYNA levels have been found in both cerebral spinal fluid (Erhardt et al. 2001) and *postmortem* brain tissue of schizophrenic patients (Schwarcz et al. 2001). Thus, a disruption between KYNA, Glu, and DA levels may exacerbate dysfunctional cortical and subcortical communication, contributing to inappropriate information processing in neuropsychiatric disorders like SP.

6 Schizophrenia and KYNA

Psychiatric disorders are associated with a mild proinflammatory state. Proinflammatory mediators could activate the Trp breakdown, causing dysregulation of KP, which results in hyper- or hypofunction of active metabolites. In turn, these changes are associated with neurodegenerative and other neurological disorders, as well as with psychiatric diseases such as schizophrenia (SP) (Schwarcz et al. 2012).

SP is one of the main psychiatric disorders reported and has been described as a psychotic disease characterized by impaired cognition and accompanied by emotional and behavioral alterations. Major symptoms are auditive hallucinations, para-

noid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction (Myint 2012). Dysfunctional interactions between neurotransmitter systems and brain regions are implicated in SP. Cognitive impairments in SP are now hypothesized to be due to primary neuronal dysfunctions rather than chronicity or neurodegeneration (Hoff et al. 1999; Rajkowska et al. 1998). The neurochemistry of cognitive impairment in SP invokes distinct interdependent changes in major neurotransmitter systems within the prefrontal cortex (PFC). Namely, changes in cholinergic, glutamatergic, dopaminergic, and GABAergic functions are critically involved in the physiopathology of SP (Sarter et al. 2005; Lewis and Moghaddam 2006). Recent studies suggests that KYNA, the only endogenous NMDAr antagonist identified up to now—and also an antagonist for the nicotinergic acetylcholine receptor—might be involved in prefrontal dysfunctions in SP. Since its levels are elevated in the PFC of individuals with this disorder, with Brodmann areas 9 and 10 increasing by 46.8 % and 83.4 %, respectively, versus control (Sathyasaikumar et al. 2011), thereby leading to the concept that changes in KYNA concentrations might contribute to cognitive dysfunction associated with this disorder. Despite the fact that it has been argued that the physiological levels of KYNA could be below those levels needed to exert antagonism on glutamatergic receptors (K_D~ 8 μM; Ganong and Cotman 1986; Kessler et al. 1989), in some specific places of synapses, KYNA levels could be sufficient to exert responses in nerve tissue (Scharfman et al. 2000). Experiments in rodents have demonstrated that even relatively minor elevations in KYNA levels in the PFC cause a decrease in the extracellular levels of Glu, acetylcholine, and DA known to be associated with cognitive dysfunctions. Interestingly, these effects are bidirectional since a selective reduction in KYNA formation substantially enhances the extracellular presence of these classic neurotransmitters (Wu et al. 2007, 2010; Zmarowski et al. 2009).

Several other studies have shown that increasing endogenous KYNA concentrations induced by L-KYN administration results in spatial and contextual learning deficits in rats (Chess et al. 2007; 2009) as well as impaired sensory gating, prepulse inhibition, and attention in adult rats (Shepard et al. 2003; Erhardt et al. 2004; Chess and Bucci 2006). Noteworthy, when L-KYN is administered to young adult rats (equivalent to adolescence, a critical period for brain development), the increase in KYNA concentrations impact cognitive functions in adulthood and exhibited deficits in contextual fear memory, while impaired on a novel object recognition memory task. Recently, it was also showed that prolonged KYN treatment during prenatal and early postnatal development in rats increased the KYNA levels, which was accompanied by a reduction in basal levels of extracellular glutamate in adult rats. Additionally, it was observed impaired performance in passive avoidance and the Morris water maze (Pocivavsek et al. 2012). The implications of these findings lie in the fact that exposure to high levels of KYNA results in inhibition of NMDAr and/or α7nAChR during critical stages of the development, thereby exerting lasting impacts on brain morphology and/or cognitive functions during adulthood, contributing to cognitive deficits typically observed in SP (Akagbosu et al. 2012).

In this context, epidemiological evidence indicates that microbial pathogens and parasitic infections may contribute to cognitive impairments in patients with

SP. However, the precise mechanisms whereby the parasite impacts cognition remain poorly understood. Infection during pregnancy in mothers of offspring later developing SP has been repeatedly described (Mednick et al. 1988; Brown et al. 2004; Buka et al. 2001). In a follow-up study of children who had suffered from bacterial meningitis from age 0 to 5 years during an epidemic in Brazil, a fivefold increased risk for developing psychoses later on was observed (Gattaz et al. 2004). Since the development of the brain is not finalized at birth, but is still ongoing for the first years of life, an infection during early childhood is still in accordance with the assumption that an infection-triggered disturbance in brain development plays a pivotal role in SP (Muller and Schwarz 2006). Considerable body of evidence links *Toxoplasma gondii* infection to an increased incidence of schizophrenia (Dickerson et al. 2007; Mortensen et al. 2007; Hinze-Selch et al. 2007; Schwarcz and Hunter 2007). An interesting study measured antibody titers against infectious agents not only in the serum but also in the cerebrospinal fluid of individuals with recent onset of SP. Titers against cytomegalovirus and *T. gondii* were significantly increased (Leweke et al. 2004). The link between *T. gondii* and changes in glutamatergic neurotransmission remains poorly studied, but KYNA has already been hypothesized to be a pathogenic link between *T. gondii* infection and cognitive impairment in SP (Schwarcz and Hunter 2007). Experimental studies have shown that diminishing elevated KYNA levels is predicted to ameliorate cognitive deficits. Knockout mice with deletion of the enzyme that converts kynurenine into KYNA, KAT II, express lower levels of KYNA and perform better in cognitive test when compared to control mice (Potter et al. 2010). Because rodents infected with *T. gondii* and patients with SP exhibit increased KYNA levels in the brain (Schwarcz and Hunter 2007; Kannan and Pletnikov 2012), one could predict that reduction of levels of this NMDAr antagonist may have therapeutic effects.

A disruption of the immune response is associated with an altered balance in KP metabolism as well as oxidative stress. Clinical and preclinical investigations of the actions of antioxidative defense systems in the brain suggest several ways in which ongoing oxidative stress might impact the occurrence and course of SP. A recent meta-analysis indicated that there is an increase in the levels of lipid peroxidation products and NO in SP, while SOD activity was found to be significantly decreased in this disorder (Zhang et al. 2010). These findings show an increase of superoxide and other ROS and correlated with an increased expression of TDO compared to IDO in SP patients (Miller et al. 2004). Interestingly, TDO2 mRNA is elevated in the brain of individuals with SP, and a concomitant increased density of TDO2-immunopositive astroglial cells is seen in white matter of these patients (Miller et al. 2004). Because TDO is one of the upstream enzymes responsible for the biosynthesis of KYNA, this enhanced expression could conceivably lead to an elevation of KYNA levels in the diseased brain, therefore playing a part in the pathophysiology of this disorder.

Further evidence favors the concept that high levels of KYNA are implicated in SP: a recent study revealed distinct abnormalities in KP enzymes in BA9 and BA10 cortical regions (Sathyasaikumar et al. 2011). While the activity of KATII was in the normal range, a significant decrease in KMO activity in the PFC of individuals with

SP was observed. Of note, this reduction was not accompanied by decreased kynureninase activity. The activity of 3-HAO, which catalyzes the formation of QUIN from 3-HANA, was found to be reduced in the PCF. Decreased 3-HAO activity might account for the elevation in tissue levels of 3-HANA in SP, which was recently demonstrated in the anterior cingulate cortex (Miller et al. 2008) and might affect the redox status of neurons and glial cells in the area. This KMO downregulation provides an explanation for the increased levels of KYNA consistently found in *postmortem* brain tissue (Schwarcz et al. 2001) as well as in the cerebrospinal fluid of individuals with SP (Nilsson et al. 2005).

Altogether, this body of evidence suggests an impact of KYNA levels on cognitive deficit in SP; however, the routes by which KYNA production is increased in SP remain unclear since the "canonic" pathway involving KATII activity is not altered. In this regard, some studies have shown that KYNA can be formed by the nonenzymatic oxidation of kynurenine and Trp via indole-3-pyruvic acid (Politi et al. 1991), a reaction which is increased by oxidative stress. Increased levels of nitric oxide have been noticed after brain injury, and this can inhibit SOD. The resulting increase in superoxide anions could, in turn, oxidize indolepyruvate to KYNA, consistently with reports that nitric oxide donors increase KYNA production (Luchowski and Urbanska 2007). The close correlation between inflammation, oxidative stress, and KP and the impact that these components exert in neurotransmission are likely to be involved in the pathogenesis of SP.

7 Concluding Remarks

In recent years, different groups have investigated the impact of KP metabolites on SP—especially KYNA—and its role on the hypoglutamatergic function observed in patients with this disorder. Notably, the upregulation of KYNA levels in SP is often accompanied by increased tissue levels of kynurenine, the immediate KYNA bioprecursor (Schwarcz et al. 2001). Different mechanisms could be accounting for KYNA formation in SP: (1) increased TDO activity, (2) decreased KMO activity, (3) early infectious/inflammatory events affecting the brain, and (4) altered redox status. Taken together, these changes would serve to hypothesize the following order of events (summarized in Fig. 2), potentially leading to the pathological status involved in SP: First, an early inflammatory process probably due to an infectious origin would trigger metabolic alterations in peripheral and central KP, thus increasing the Trp and kynurenine availability in the brain, together with increased TDO and IDO activities and a concurrent KMO activity. The scenario produced by these changes would also imply increased levels of KYNA apparently produced by mechanisms other than KATs activation, i.e., via ROS formation and oxidative modifications, whose origins are either Trp conversion into 3-indole-pyruvic acid—further leading to KYNA when reacting with ROS—or kynurenine conversion—which, in the presence of H_2O_2 and a peroxidase, yields KYNA formation. In addition, if kynurenine

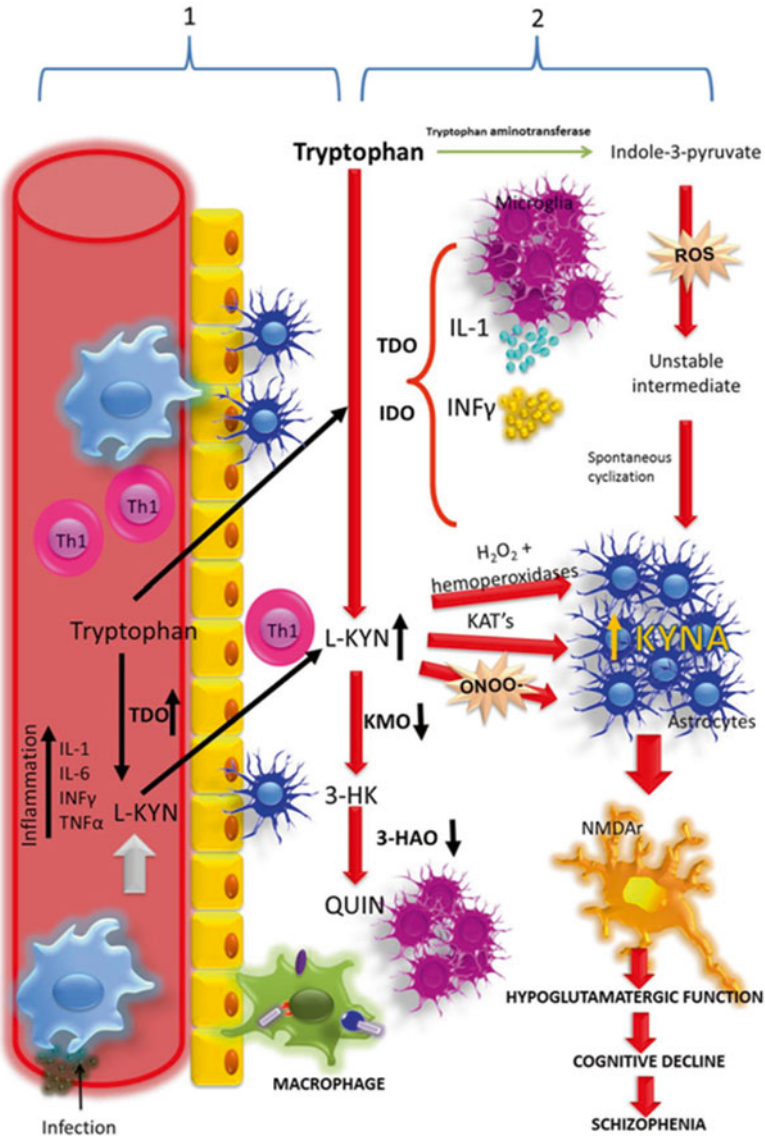

Fig. 2 Schematic representation of the mechanism underlying the events involved in the increases of KYNA levels in SP. In step 1, an inflammatory process due to possible infection or stress favors KP and its vulnerable brain barrier allowing passage of metabolites formed in the periphery to the CNS, in such events possibly early impact modified in later stages (2), in which the increase in KYNA levels seems to be the key of cognitive impairment present in patients with SP

actions recruit scavenger properties, as already reported (Ugalde-Muñiz et al. 2012), then kynurenine oxidation itself could account for KYNA formation (Lugo-Huitrón et al. 2011b). The latter would, in turn, explain why, during the early stages of SP, the levels of kynurenine and KYNA are both substantially increased, which also

matches with a hypoglutamatergic function typically observed in cognitive decline seen in SP patients. The precise degree of involvement of these events on the onset of SP constitutes a fertile line of research to explore in the next years. In the meantime, it is clear that KYNA hypothesis in SP is a promising tool to develop therapeutic designs for this and other psychiatric disorders.

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