J Neural Transm (2012) 119:133–139
DOI 10.1007/s00702-011-0763-x

Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery

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Received: 27 October 2011 / Accepted: 25 December 2011 / Published online: 4 January 2012

Abstract It is usually assumed that kynurenic acid (KYNA) modifies neuronal function because it antagonizes the glycine site of the NMDA receptors and/or the neuronal cholinergic $\alpha 7$ nicotine receptors. It is not clear, however, whether the basal levels of KYNA found in brain extracellular spaces are sufficient to interact with these targets. Another reported target for KYNA is GPR35, an orphan receptor negatively coupled to G_i proteins. GPR35 is expressed both in neurons and other cells (including glia, macrophages and monocytes). KYNA affinity for GPR35 in native systems has not been clarified and the low-affinity data widely reported in the literature for the interaction between KYNA and human or rat GPR35 have been obtained in modified expression systems. Possibly by interacting with GPR35, KYNA may also reduce glutamate release in brain and pro-inflammatory cytokines release in cell lines. The inhibition of inflammatory mediator release from both glia and macrophages may explain why KYNA has analgesic effects in inflammatory models. Furthermore, it may also explain why, KYNA administration (200 mg/kg ip × 3 times) to mice treated with lethal doses of LPS, significantly reduces the number of deaths. Finally, KYNA has been reported as an agonist of aryl hydrocarbon receptor (AHR), a nuclear protein involved in the regulation of gene transcription and able to cause immunosuppression after binding with dioxin. Thus, KYNA has receptors in the nervous and the immune systems and may play interesting regulatory roles in cell function.

Keywords Kynurenine · NMDA · Glutamate receptors · Nicotinic receptors · GPR35 · AHR

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Introduction

Once upon a time, kynurenic acid (KYNA) was considered one of the numerous inert tryptophan metabolites present in mammalian urines. Its name means indeed "acid in dog urines" and it was coined by Liebeg in the second half of the 19th century. Its molecular structure was clarified and the compound was chemically synthesized at the beginning of the XX century (Homer 1914). The metabolic steps leading from tryptophan to KYNA were identified in the course of studies performed during the first half of the last century in order to clarify NAD or NADH formation from tryptophan. They are: (1) opening of the indole ring with formyl-kynurenine formation, (2) rapid and almost complete hydrolysis of formyl-kynurenine into kynurenine, (3) transamination of kynurenine into KYNA (Moroni 1999).

The first step of the pathway is catalyzed by either tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) (Hirata and Hayaishi 1975), the second is catalyzed by formamidase, an abundant protein (Mehler and Knox 1950) not particularly studied in mammals (Dobrovolsky et al. 2005) and the third by a family of kynurenine amino-transferases (KATs). These transaminases have a rather low affinity for their substrate (in the mM range) and therefore kynurenine availability is the main factor controlling the rate of KYNA formation and its local concentration. The most studied KATs are KAT I

(identical with glutamine transaminase K, EC 2.6.1.64) and KAT II (identical with α-aminoadipate aminotransferase, EC 2.6.1.7). KAT III and other transaminases such as mitochondrial aspartate aminotransferase (EC 2.6.1.1) may also form KYNA, but have not been particularly investigated in this contest (Rossi et al. 2008). Gene targeting studies have shown that KAT II knockout mice have reduced brain KYNA levels and a number of behavioral changes such as enhanced hippocampal plasticity and improved cognitive behavior (Potter et al. 2010), suggesting that in the brain, KAT II is the main responsible for KYNA synthesis and that KYNA plays an important role in modulating neural plasticity and cognition.

Current interest in "kynurenines" actions in brain originated in the late 70s when Lapin and its group, reported from Saint Petersburg (URSS) that systemic or intracerebral administration of KYNA could dampen quinolinic acid-induced seizures in mice and rats (Lapin 1976, 1980). The observation that two different tryptophan metabolites such as quinolinic and kynurenic acids, formed in the same metabolic pathway, could either cause or antagonize convulsions seemed particularly interesting. In the early 80s it was observed that while quinolinic acid could stimulate, KYNA could selectively antagonize glutamate receptors of NMDA type (Perkins and Stone 1982) and in a similar manner, while quinolinic acid could cause excitotoxicity (Schwarcz et al. 1983), KYNA could reduce excitotoxic neuronal damage in rat brain (Foster et al. 1984). A few years later, it was shown that KYNA was present in the central nervous system of different animal species, including man, and that its extracellular or cerebrospinal fluid concentrations ranged from 15 to 150 nM (Moroni et al. 1988b; Turski et al. 1988; Swartz et al. 1990). It was also shown that brain KYNA is mostly synthesized in glial cells, has a relatively fast turnover rate and significantly accumulates during the aging process (Moroni et al. 1988a). In this brief review, we will report some of the data on the possible mechanism(s) of KYNA action with particular attention to the experiments performed in our laboratory.

KYNA: mechanism of action in the brain

It has been repeatedly shown that KYNA is a potent antagonist of the glycine allosteric site the NMDA receptor complex and for several years it was assumed that the interaction between KYNA and the NMDA receptor complex could have a physiological role in brain function (Stone 1993). However, it should be noted that the extracellular concentrations of KYNA in mammalian brains are in the low nM range while KYNA affinity for the glycine site of the NMDA receptor complex is approximately 10–20 μM. It seems therefore possible that other targets are responsible of the electrophysiological and behavioral actions observed when brain KYNA levels are increased or decreased. Indeed, a modest increase of KYNA extracellular concentrations in brain has been associated with a reduction of the rate of cell firing in the rat locus coeruleus (Erhardt et al. 2000) and with a number of behavioral effects (reduced locomotor activity, mild analgesia, control of seizures and prevention of excitotoxic neuronal damage) suggesting that nM concentrations of KYNA may reduce the activity of brain excitatory transmission (Russi et al. 1989, 1992; Moroni et al. 1991; Vecsei and Beal 1991; Vecsei et al. 1992; Carpenedo et al. 1994; Nemeth et al. 2004). It has also been demonstrated that a 2 or 3-fold elevation of brain KYNA levels significantly reduces post-ischemic brain damage in models of focal or global brain ischemia in vivo and in organotypic hippocampal slice cultures exposed to oxygen and glucose deprivation in vitro (Cozzi et al. 1999; Carpenedo et al. 2002).

An increase of brain KYNA levels may be obtained by administering direct or indirect precursors, transport inhibitors or inhibitors of kynurenine 3-monooxygenase (KMO) the most abundant of the kynurenine metabolizing enzymes. No matter of the approach used, a mild increase of brain KYNA concentration reduces excitatory transmission and this may be evaluated with biochemical, electrophysiological, histological or behavioral methods (Bacciottini et al. 1987; Nozaki and Beal 1992; Chiarugi et al. 1996). Recently, a very elegant study reported that inhibition of kynurenine 3-monooxygenase in peripheral organs, by increasing blood kynurenine levels and brain KYNA content, significantly reduced neurodegeneration in different transgenic models of Huntington's and Alzheimer's diseases (Zwilling et al. 2011). Similar results have been obtained in a drosophila model of Huntington chorea (Campesan et al. 2011).

A possible explanation of all these findings is reported in Fig. 1: KYNA, infused through a microdialysis cannula in the rat caudate at low nM concentrations drastically reduces extracellular brain glutamate content. This robust decrease of excitatory transmitter levels in brain extracellular spaces could explain most of behavioral, electrophysiological and neuroprotective effects of KYNA. The molecular mechanism(s) of these effects, however, remain to be clarified. Since a reduction of glutamate extracellular concentrations comparable with that caused by KYNA (30–100 nM) may be obtained with type 2/3 metabotropic glutamate receptors (mGluR2/3) agonists, we assumed that KYNA could interact with these sites. However, KYNA does interact neither with native mGlu2/3 receptors nor with cloned receptors permanently expressed in baby hamster kidney (BHK) cells (Carpenedo et al. 2001).

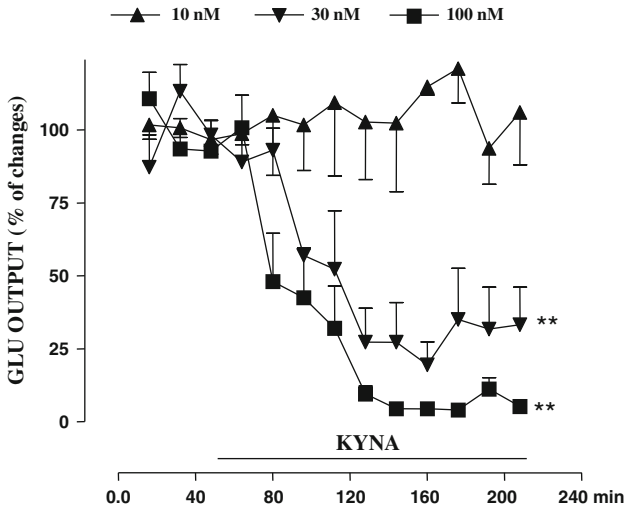

Fig. 1 Effects of local administration of KYNA through the microdialysis cannula in the rat caudate on extracellular glutamate levels. KYNA was added to the dialysis fluid 1 h after the beginning of the experiments and its application continued for 3 h. Each point is the mean value plus or minus of at least six animals. $^{**}P < 0.01$ versus saline. Basal glutamate levels were: 210 ± 50 pmol/15 min. (data from Carpenedo et al. 2001)

It has also been demonstrated that KYNA antagonizes α7 cholinergic nicotine receptors that are mostly located on pre-synaptic terminals (Hilmas et al. 2001) and it has been proposed that the reduced levels of glutamate in the extracellular spaces found in KYNA treated animals are due to inhibition of these receptors. However, KYNA affinity for α7 receptors is still rather low (μM levels) and certainly not in the range of the concentrations able to reduce glutamate release (low nM). Furthermore, other α7 nicotine antagonists have some, but not all the actions of KYNA on excitatory transmitter release (Carpenedo et al. 2001). Thus, the reduction of glutamate concentration in the extracellular spaces cannot be exclusively ascribed to KYNA interaction with α7 cholinergic nicotine receptors.

Besides interacting as an antagonist with the glycine site of the NMDA receptor and with cholinergic α7 nicotine receptors, KYNA has been proposed as the endogenous agonist of GPR35, a G_i-protein coupled receptor (Wang et al. 2006). Another KYNA suggested target is the aryl hydrocarbon receptor (AHR), a nuclear receptor able to recognize aromatic hydrocarbons and 2,3,7,8-tetrachlorodibezo-*p*-dioxin (DiNatale et al. 2010) (see Table 1). Finally, large concentrations of KYNA (in the range of 100–300 μM) may have direct antioxidant properties and are able to inhibit oxidative stress because of free radical scavenging activity (Lugo-Huitron et al. 2011). It is unlikely that concentrations above 100 μM may be locally reached under either physiological or pathological conditions.

Table 1 Possible kynurenic acid targets

Antagonism	IC50 (μM)	References
Glycine site NMDA receptor	10–30	(Kessler et al. 1989)
Nicotinic α7	1–8	(Hilmas et al. 2001)
Glutamate site of AMPA or NMDA	300	(Perkins and Stone 1982)
Agonism		
GPR35	0.1–30	(Wang et al. 2006)
AHR	NA	(DiNatale et al. 2010)

NA not available

KYNA actions in glia and other non-neuronal cells

As mentioned above, KYNA may activate GPR35, a protein present in the brain but especially abundant in the dorsal root ganglia and in cells of the immune system. Activation of GPR35 inhibits LPS-induced TNFα release from macrophages (Wang et al. 2006) and a number of other Ca^{2+}-dependent release processes which may include inhibition of transmitter release (Ohshiro et al. 2008). Again, it should be mentioned that KYNA affinity for cloned human or rat GPR35 is relatively low (EC50 between 10 and 100 μM) and certainly rather distant from the concentrations that, when added to the microdialysis probe, drastically reduce glutamate levels in brain extracellular spaces. In our opinion, however, the published affinity of KYNA for mammalian GPR35 is artificially low. The available data have been generated in transfected systems in which the protein has been linked with tags and with fluorescent peptides (Jenkins et al. 2011; Milligan 2011) or after transfection with modified G-proteins (Zhao et al. 2010; Jenkins et al. 2011). Therefore, we investigated KYNA effects in cell types expressing native GPR35 associated to G_i-proteins on the release of molecules involved in neuroinflammation and neurorepair processes (Fig. 2). We previously reported that in microglial cell

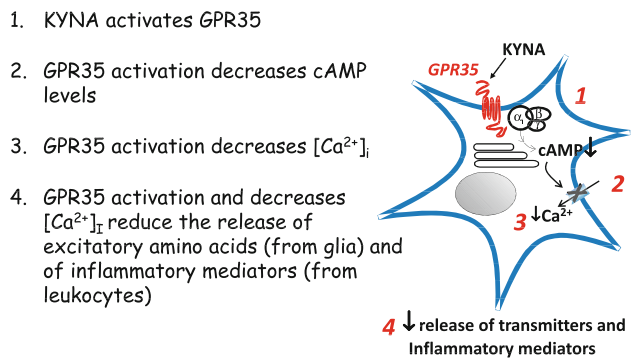

Fig. 2 Hypothesis on the mechanism of the action of KYNA and its interaction with GPR35: inhibition of transmitter and inflammatory mediator release

lines and in transformed fibroblasts (NIH 3T3 cells), KYNA inhibits the heath shock- or starvation-induced release of active compounds such as FGF-α or interleukin-1 with an IC_{50} of approximately 0.1 μM (Di Serio et al. 2005). We also observed that KYNA reduces, in a concentration-dependent manner, the LPS-induced secretion of high-mobility group box 1 protein (HMGB1) without causing obvious changes in its expression in a murine macrophage cell line (RAW264.7) (Moroni et al. 2007). HMGB1 is a 215 amino acid polypeptide belonging to the alarmin group and secreted through non-classical mechanisms similar to those mediating FGF or interleukin-1 release (Tarantini et al. 2001). In astrocytes, microglial cells and neurons exposed to ischemic challenges, HMGB1 is released and cause activation of Receptor for Advanced Glycation End products (RAGE) contributing to post-ischemic brain damage (Faraco et al. 2007). It may be proposed, therefore, that a reduced HMGB1 release from cells of the neurovascular unit could be one of the mechanisms of KYNA neuroprotective actions in stroke models.

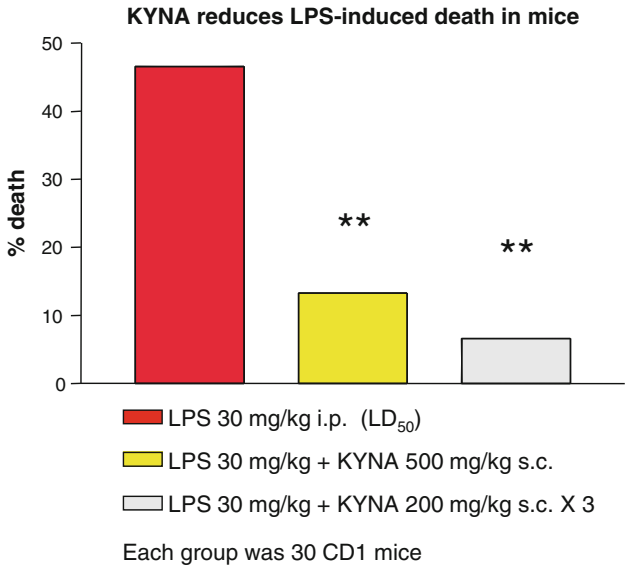

Fig. 3 KYNA (200 mg/kg administered at 0; 3 and 6 h after LPS) reduces the LPS-induced death of mice. $^{**}P < 0.01$ versus LPS

Since KYNA attenuates the release of several pro-inflammatory cytokines including TNFα and HMGB1 from macrophages as well as this release is considered a key event in the pathological process leading to irreversible septic shock, we next studied the effects of KYNA administration on LPS-induced death in mice. KYNA administration (200 mg/kg × 3) resulted in elevated plasma KYNA levels (Moroni et al. 2007) and in drastic reductions of total death rate (Fig. 3). The effect was rather specific, since xanthurenic acid, a metabolite having physical and chemicals properties comparable to those of KYNA was inactive (Moroni et al. 2007). Figure 4 shows that KYNA-treated mice had a drastically reduced serum TNFα level after the LPS challenge. It has also been shown that LPS itself and pro-inflammatory cytokines released during the first phase of septic shock may induce the expression of nitric oxide synthase and cause the accumulation of large quantities of nitric oxide (NO) in plasma/serum. This accumulation seems to play a crucial role in LPS-induced death (Thiemermann and Vane 1990; Julou-Schaeffer et al. 1990). KYNA drastically reduced the accumulation of NO in the serum of LPS treated mice (Fig. 4). This effect was not mediated by NMDA receptors because neither MK-801, a non-competitive antagonist, nor AP5, a competitive antagonist, used at fully active dosages, reduced LPS mortality.

In separate experiments we found that KYNA concentrations reached in plasma of treated animals were in the low μM range. KYNA administration seems therefore a rather simple and feasible approach to reduce the number of deaths in a septic shock model. GPR35, activation, and

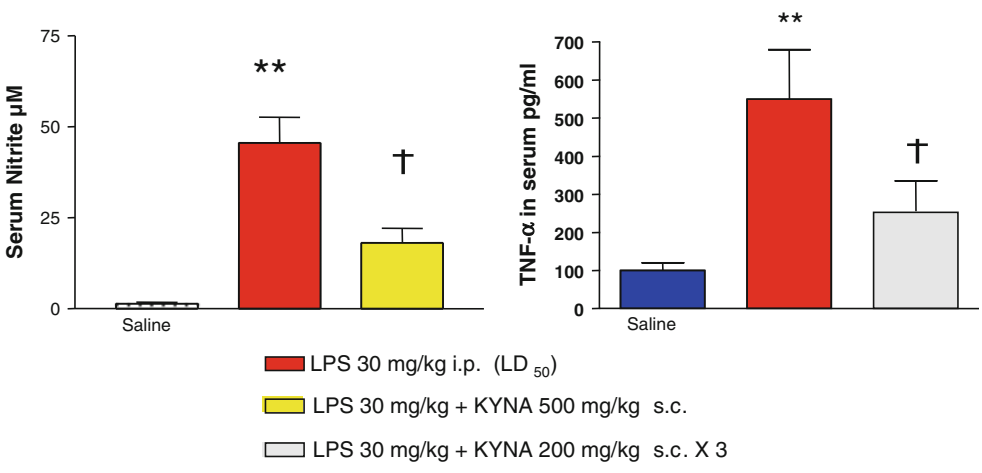

Fig. 4 KYNA administration prevents the increase of serum TNFα and NO levels in LPS-treated mice. $^{**}P < 0.01$ versus saline; $^{\dagger}P < 0.01$ versus LPS only. (Data from Moroni et al. 2007)

the reduced output of inflammatory mediators, is a reasonable explanation of those results. The possibility of obtaining high-affinity agonists and antagonists for GPR35 seems another obvious strategy to be followed for the control of the pathological events associated with acute systemic inflammation and to reduce the number of death in septic shock.

Since GPR35 is largely expressed in the rodent dorsal root ganglia we also investigated the possibility of activating this receptor to reduce pain in inflammatory states. We used the "writhing test" induced by acetic acid ip. injection in mice as a model of inflammatory pain and we observed that there is an inverse correlation between plasma KYNA levels and the number of writhes induced by acetic acid. In a similar manner behave other GPR35 agonists suggesting that GPR35 could be a good target to dampen inflammatory pain states (Cosi et al. 2011).

KYNA and aryl hydrocarbon receptor (AHR)

It has been recently reported that KYNA may be one of the endogenous ligands of the aryl hydrocarbon receptor (AHR), a ligand activated transcription factor of the basic helix-loop-helix (bHLH) Per/ARNT/Sim family (Denison and Nagy 2003). Until recently, AHR was considered a xenobiotic receptor regulated through the binding of several exogenous compounds such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, a toxic chemical that powerfully suppresses antibody and cellular immune responses, modulates the synthesis of inflammatory mediators, stimulates carcinogenesis and promotes tumor outgrowth (DiNatale et al. 2010). Interestingly, it has been recently shown that kynurenine is also able to activate AHR responses (Nguyen et al. 2010; Opitz et al. 2011). The relative affinity of kynurenine or KYNA for this receptor is not available. In fact while in hepatic cells in cultures, DiNatale et al. (2010) report that KYNA is a rather potent agonist, Opitz et al. (2011), working in gliomas and other tumor cells, suggest that kynurenine is more active than KYNA in performing this task. Possibly AHR is able to interact with several "kynurenines" and to promote the generation of immune-suppressive T cells that support cancer development (Mezrich et al. 2010). The binding of the "kynurenines" to AHR causes the receptor to move into the nucleus where it binds target genes and activates their transcription leading to tumor progression (Stevens et al. 2009). These findings open a number of questions on the activities that kynurenine metabolites have in cancer biology and in immunology. In other words, KYNA-induced activation of AHR and the effects that may derive from increased kynurenine/KYNA availability may increase the risk of developing malignancies? This should be considered when procedures aimed at increasing blood and brain levels of these tryptophan metabolites are proposed. On the other end, the anti-inflammatory actions of kynurenines and KYNA due to a controlled activation of AHR may be exploited for the treatment of autoimmunity or other immune disorders?

Conclusion

Multiple mechanisms may mediate KYNA actions in brain and periphery. While most of the laboratories assume that KYNA actions may be mostly explained because of its antagonism with both the glycine site of the NMDA receptors and the cholinergic $\alpha 7$ nicotine receptors, a number of other targets have been recently proposed and should be taken into consideration.

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