**Review**

**Cinnabarinic acid and xanthurenic acid: two kynurenine metabolites that interact with metabotropic glutamate receptors.**

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**Running head:** Cinnabarinic acid, xanthurenic acid, and glutamate receptors

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**Abstract**

Cinnabarinic and xanthurenic acids are kynurenine metabolites generated by oxidative dimerization of 3-hydroxyanthranilic acid and transamination of 3-hydroxykynurenine, respectively. Recent evidence suggests that both compounds can affect brain fuction and neurotransmission and interact with metabotropic glutamate (mGlu) receptors. Cinnabarinic acid behaves as an orthosteric agonist of mGlu4 receptors, whereas some of the *in vitro* and *in vivo* effects produced by xanthurenic acid appear to be mediated by the activation of mGlu2 and mGlu3 receptors. Cinnabarinic acid could play an important role in mechanisms of neuroinflammation acting as a linking bridge between the immune system and the CNS. Xanthurenic acid has potential implications in the pathophysiology of schizophrenia and is a promising candidate as a peripheral biomarker of the disorder. The action of cinnabarinic acid and xanthurenic acid may extend beyond the regulation of mGlu receptors and may involve several diverse molecular targets, such as the aryl hydrocarbon receptor for cinnabarinic acid and vesicular glutamate transporters for xanthurenic acid. The growing interest on these two metabolites of the kynurenine pathway may unravel new aspects in the complex interaction between tryptophan metabolism and brain function, and lead to the discovery of new potential targets for the treatment of neurological and psychiatric disorders.

**Key words:** cinnabarinic acid **-** xanthurenic acid **-** metabotropic glutamate receptors – neuroinflammation - schizophrenia

**1. Introduction**

The kynurenine pathway of tryptophan metabolism generates a series of neuroactive compounds of which quinolinic acid and kynurenic acid gained popularity in neuroscience for their ability to activate and inhibit NMDA receptors, respectively (Stone and Perkins, 1981; de Carvalho et al. 1996; Parsons et al., 1997; Schwarcz et al., 2012). Hence, most of the studies on the kynurenine pathway in the CNS have focused on the role of kynurenic and quinolinic acids in physiology and pathology, and on the metabolic processes leading to the synthesis of these two compounds, i.e., the direct transamination of L-kynurenine into kynurenic acid catalyzed by kynurenine aminotransferases (KATs), and the sequential transformation of L-kynurenine into 3-hydroxykynurenine, 3-hydroxyanthranlic acid, and quinolinic acid. These metabolic reactions are compartimentalized in the CNS, with production of 3-hydroxykynurenine, 3-hydroxyanthranilic acid,and quinolinic acid occurring in microglia, and KAT-induced transamination of L-kynurenine into kynurenic acid occurring in astrocytes (Schwarcz and Pellicciari, 2002; Guillemin et al., 2004; Guidetti et al., 2007a,b; Amori et al., 2004; Han et al., 2009) Kynurenine monooxygenase (KMO), the enzyme that transforms L-kynurenine into 3-hydroxykunurenine, has been the subject of extensive investigation, and represents a promising candidate drug target in the treatment of CNS disorders (Wonodi and Schwarcz, 2010; Schwarcz et al., 2012). Compounds that are generated « horizontally » by 3-hydroxykynurenine and 3-hydroxyanthranilic acid, i.e. xanthurenic and cinnabarinic acids, respectively (Fig. 1), have been considered as « by products » of the kynurenine pathway, with little or no interest for the physiology and pathology of the CNS. However, recent findings suggest that cinnabarinic and xanthurenic acids are neuroactive compounds that are able to modulate, directly or indirectly, metabotropic glutamate (mGlu) receptors. These receptors form a family of eight subtypes, of which the mGlu4 receptor is targeted by cinnabarinic acid, whereas mGlu2 and mGlu3 receptors are involved in the action of xanthurenic acid (see below). mGlu2, mGlu3, and mGlu4 receptors are coupled to Gi/Go proteins and are preferentially localized at presynaptic nerve terminals, where they negatively regulate neurotransmitter release (reviewed by Nicoletti et al., 2011). mGlu4 receptors are also expressed by antigen-presenting cells, and their activation drives T cell differentiation into regulatory T (Treg) cells, thereby restraining autoimmunity and neuroinflammation (Falarino et al., 2010). The interaction with mGlu receptors, as well as other emerging mechanisms (e.g. inhibition of vesicular glutamate transporters by xanthurenic acid and activation of the aryl hydrocarbon - Ah - receptor by cinnabarinic acid) have generated new interest in these two kynurenine metabolites. Cinnabarinic acid (2-amino-3-oxo-3H-phenoxazine-1,9-dicarboxylic acid), which is responsible for the anitimicrobial activity of the fungus, *Pycnoporus cinnabarinus* (Eggert et al., 1997), is generated from enzymatic and non-enzymatic oxidation of 3-hydroxyanthranilic acid (Rao, 1966; Ogawa et al., 1983; Christen et al., 1992). Xanthurenic acid is formed by transamination of 3-hydroxykynurenine (Malina and Martin, 1996). In rat and human brain, transamination of 3-hydroxykynurenine into xanthurenic acid is catalyzed by type-2 kynurenine aminotransferase (Sathysaikumar et al., 2014), the same enzyme that converts kynurenine into kynurenic acid (reviewed by Schwarcz et al., 2012).

This review will focus on recent findings highlighting a potential role for cinnabarinic acid and xanthurenic acid in CNS physiology and pathology focusing on the possible role of mGlu receptors in the mechanism of action of these compounds (see Table 1).

**2. Cinnabarinic acid**

***2.1 Overview***

Recent findings led to the identification of two novel receptor targets for cinnabarinic acid: (i) the mGlu4 receptor; and (ii) the aryl hydrocarbon (Ah) receptor. Interestingy, both receptors have been implicated in mechanisms that lie at the core of neuroinflammation, by regulating the bidirectional communication between antigen presenting cells (APCs) and T lymphocytes at the immunological synapse (Stevens et al., 2009; Esser et al., 2009; Fallarino et al., 2010; Volpi et al., 2012; Quintana, 2013; Hanieh 2014; Nguyen et al., 2014).

***2.2 Activation of mGlu4 receptors***

In collaboration with the research groups of Jean-Phlippe Pin and Cyrille Goudet (University of Montpellier, France), and Francine Acher (University Renè Descartes, Paris, France) we have found that cinnabarinic acid behaves as a weak orthosteric agonist of mGlu4 receptors, with no activity at other mGlu receptor subtypes (Fazio et al., 2012). mGlu4 receptors are coupled to Gi/o GTP-binding proteins, and are localized on presynaptic terminals where they negatively regulate neurotransmitter release (reviewed by Nicoletti et al., 2011). Selective positive allosteric modulators (PAMs) of mGlu4 receptors are under development for the treatment of Parkinson’s disease (reviewed by Nickols and Conn, 2014; Walker and Conn, 2015), and are potential candidate drugs for the treatment of neuropathic pain (Goudet et al., 2008). Of note, mGlu4 receptors are also expressed by APCs and T lymphocytes (Fallarino et al., 2010; see below).

Cinnabarinic acid acts as a partial agonist in cell clones expressing mGlu4 receptors by interacting with the glutamate binding pocket localized in the N-terminus Venus Fly Trap domain of the receptor. In addition, cinnabarinic acid inhibits cAMP formation in cultured cerebellar granule cells, which are known to express large amounts of mGlu4 receptors (Santi et al., 1994), and the cAMP response to low concentrations of cinnabarinic acid is abolished in cultures prepared from mGu4 receptor knockout mice (Fazio et al., 2012). Cinnabarinic acid attenuates excitotoxic neuronal death in cultured cortical cells, and protects nigro-striatal neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity when locally infused into the mouse external globus pallidus (Fazio et al., 2012), mimicking the action of conventional mGlu4 receptor agonists (Maj et al., 2003; Battaglia et al., 2006). These findings indicate that cinnabarinic acid is able to activate native mGlu4 receptors in the CNS. Perhaps mGlu4 receptors in the CNS have a high receptor reserve that permits receptor activation in response to a partial agonist. However, most of the effects seen in cultured neurons require concentrations of cinnabarinic acid >10-30 M (Fazio et al., 2012), and this casts doubt on the physiological relevance of the interaction beween cinnabarinic acid and neuronal mGlu4 receptors. Under normal conditions, brain cinnabarinic acid is below the detection levels in the mouse brain, wheres it can be detected in peripheral organs, such as the kidney, lung, liver, and spleen (Fazio et al., 2012). However, brain cinnabarinic acid levels levels dramatically increase (up to >150 pg/mg tissue) in response to systemic injection of lipopolysaccharide (LPS), which is known to cause neuroinflammation, although information on the cellular and sub-cellular distribution of cinnabarinic acid in the CNS is lacking (Fazio et al., 2012). It is possible that cinnabarinic acid formed as a by-product of the kynurenine pathway activated in response to neuroinflammation serves as an endogenous protective agent that restrains synaptopathy and neuronal damage caused by pro-inflamatory cytokines secreted by immune cells or by resident astrocytes and microglia. This attractive hypothesis warrants further investigation.

The evidence that the mGlu4 receptor is involved in mechanisms regulating the fate of T cells at the immune synapse (Fallarino et al., 2010) has provided new insights into the role played by mGlu4 receptors in neuroinflammation. The mGlu4 receptor is expressed in dendritic cells, and its activation tips the balance of Th cell differentiation in favour of a Treg immune tolerant phenotype (Fallarino et al., 2010). As a result of this mechanism, systemic treatment with the mGlu4 receptor PAM, (-)-N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC), protects mice against the development of experimental autoimmune encephalomyelitis (EAE, an experimental animal model of multiple sclerosis), whereas mice lacking mGlu4 receptors show a more severe form of EAE in response to immunization with a myelin-related antigen (Fallarino et al., 2010). A more recent study has confirmed these findings showing that compound ADX88178, a novel mGlu4 receptor PAM endowed with high potency and selectivity and optimized PK profile, protects mice against EAE and stimulates dendritic cells to produce tolerogenic cytokines, such as interleukin-10 and transforming growth factor- *via* a Gi-independent signaling pathway that involves phosphatidylinositol-3-kinase, the tyrosine kinase, Src, and type-1 indoleamine 2,3-dioxygenase (IDO-1) (Volpi et al., 2016). The evidence that activation of mGlu4 receptors directs Th differentiation toward Treg cells at the expense of Th17 cells (Falarino et al., 2010) laid the groundwork for the study of cinnabarinic acid in EAE mice. Systemic treatment of cinnabarinic acid (0.1-10 mg/kg, i.p.) protected against MOG35-55 (fragment 35-55 of the mlyelin oligodendrocyte glycoprotein)-induced EAE by boosting an immune response dominated by Treg cells (Fazio et al., 2014). However, this action of cinnabarinic acid was only partially reduced in mGlu4 knockout mice, suggesting that cinnabarinic acid recruits additional targets to regulate immune function and restrain neuroinflammation.

***2.3 Interaction with the Ah receptor***

A growing body of evidence indicates that the Ah receptor is a major target for cinnabarinic acid in the modulation of the immune system. The Ah receptor is a ligand-dependent transcription factor that owes its name to its interaction with aromatic hydrocarbons, such as benzopyrene, 3-methylcolanthrene, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Binding of aromatic hydrocarbons to Ah receptors induces the expression of genes encoding for enzymaes involved in xenobiotic metabolism, such as CYP1A1 and CYP1A2. Besides this established function, the Ah receptor has an emerging role in the regulation of the immune system promoting T cell differentiation into Treg or Th17 cells depending on the receptor ligand (reviewed by Fallarino et al., 2014). Recent evidence indicates that Ah receptor activation mediates immune tolerance to bacterial endotoxins *via* IDO-1 signaling activity (Bessede et al., 2014). The Ah receptor is targeted by a series of tryptophan metabolites that includes L-kynurenine and kynurenic acid (Mezrich et al., 2010; Nguyen et al., 2010; Maaetoft-Udsen et al., 2012; Stephens et al., 2013; Kawasaki et al., 2014; Nuti et al., 2014). Using the expansion of interleukin-22 producing cells as a read-out system, Lowe et al. (2014) have found that cinnabarinic acid acts as an endogenous agonist of Ah receptors. Interestingly, cinnabarinic acid was more effective than L-kynurenine or kynurenic acid in inducing interleukin-22 but less effective in inducing CYP1A1 in mouse or human T lymphocytes (Lowe et al., 2014). Thus, by analogy with selective estrogen and progesterone receptor modulators, cinnabarinic acid might be defined as a selective Ah receptor modulator (SAhRM) (Lowe et al., 2014). As outlined above, cinnabarinic acid becomes detectable in the brain under inflammatory conditions reaching levels >150 pg/mg tissue (Fazio et al., 2012). Considering an interstitial fluid volume of 0.2 ml/g of brain tissue (Fridèn et al., 2007), concentrations of cinnabarinic acid in the inflammed brain should be approximately 2-3 M, and these values are expected to be sufficient for an interaction between cinnabarinic acid and Ah receptors (Lowe et al., 2014; Joshi et al., 2015). Data on cinnabarinic acid levels in peripheral blood and lymphoid organs under basal and inflammatory conditions are not yet available. Mechanisms of ligand- and signaling-bias at the Ah receptors might drive the pattern of the cellular response of the Ah receptor to different kynurenine metabolites in the regulation of xenobiotic metabolism and immune function. It will be interesting to establish how mGlu4 and Ah receptors contribute to the overall response of immune cells to cinnabarinic acid taking into account that other endogenous ligands, such as glutamate for mGlu4 and tryptophan metabolites for Ah receptors, might compete with cinnabarinic acid for receptor binding, thereby shaping the cellular response to cinnabarinic acid.

Interestingly, activation of Ah receptors by cinnabarinic acid protects cultured hepatocytes against apoptosis induced by ethanol, hydrogen peroxide, and thapsigargin. This effect is mediated by the induction of stanniocalcin-2, a putative secreted glycophosphoprotein that has shown protective activity against endoplasmic reticulum and oxidative stress (Joshi et al., 2015). Whether this mechanism contributes to the neuroprotective activity of cinnabarinic acid against excitotoxic neuronal death (Fazio et al., 2012) remains to be determined.

**3. Xanthurenic acid**

***3.1 Overview***

Xanthurenic acid has been the subject of multidisciplinary studies, which address *inter alia* its role in apoptotic cell death (Malina et al., 2001 ; Malina and Hess, 2004), mitochondrial respiratory chain (Baran et al., 2016), regulation of natriuresis (Cain et al., 2007 ; Hoffman et al., 2013), regulation of insulin secretion and activity (Oxenkrug et al., 2013), and activation of gametogenesis in *Plasmodium* species (Garcia et al., 1998). Gobaille et al. (2008) have shown that xanthurenic acid is present in micromolar amounts in the rat brain, is stored in synaptic vesicles, released by depolarizing stimuli in a Ca2+-dependent fashion, and actively transported by a neuronal sodium/chloride symporter, therefore meeting the criteria to be considered as a putative neurotrasmitter. [3H]Xanthurenic acid binds to specific and saturable recognition sites in brain membranes, and specifically bound [3H]xanthurenic acid is displaced by picolinic acid and, to a lesser extent, by kynurenic acid and quinolinic acid (Taleb et al., 2012). In addition, low micromolar concentrations of xanthurenic acid enhance [35S]GTP--S binding in crude synaptosomal preparations, suggesting that xanthurenic acid binds to a G-protein coupled receptor (Taleb et al., 2012). The identity of this receptor is unknown at present.

***2.2 Interaction with group-II mGlu receptors***

A series of studies have examined the possibility that xanthurenic acid interacts with group-II mGlu receptors (mGlu2 and mGlu3 receptors). Intravenous injection or local iontophoretic application of xanthurenic acid reduced sensory inhibition of ventrobasal thalamic neurons mediated by the activation of reticular thalamic neurons (Copeland et al., 2013). Xanthurenic acid only partially mimicked the action of the prototypical mGlu2/3 receptor agonist, (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), because the action of both compounds was attenuated by the preferential mGlu2/3 receptor antagonist, 2-[(1S,2S)-2-carboxycyclopropyl]-3-(9H-xanthen-9-yl)-D-alanine (LY341495), but only the action of LY354740 was potentiated by the mGlu2 receptor enhancer, N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine (LY487379) (Copeland et al., 2013). In contrast, inhibition of synaptic transmission by xanthurenic acid was insensitive to LY341495 in rat hippocampal slices, and, as opposed to LY354740, xanthurenic acid failed to reduce paired-pulse depression in the hippocampal dentate gyrus (Neale et al., 2013). It was concluded that xanhurenic acid does not directly interact with mGlu2 or mGlu3 receptors (see below). However, xanthurenic acid displayed a high potency in activating mGlu2 and mGlu3 receptors in transfected HEK293 cells showing no activity at recombinant mGlu4- or mGlu7 receptors (Fazio et al., 2015). In mouse cortical cells, xanthurenic acid mimicked the action of mGlu2/3 receptor agonists in inhibiting cAMP formation, and its action was sensitive to LY341495 and attenuated by genetic deletion of mGlu2 receptors (Fazio et al., 2015). Specifically bound [3H]xanthurenic acid was not displaced by mGlu2/3 receptor ligands in brain membranes, and xanthurenic acid did not inhibit [3H]LY341495 binding in brain membranes (Fazio et al., 2015) and in membranes stably expressing human mGlu2 receptors (Neale et al., 2013). Interestingly, however, specific [3H]xanthurenic acid binding could be detected in membranes prepared from mGlu2- or mGlu3-expressing HEK-293 cells, but not in membranes prepared from mock cells or from mGlu4-expressing cells (Fazio et al., 2015). It is difficult to formulate a single hypothesis that may uniformely explain all these findings. It appears clear that xanthurenic acid does not directly interact with the glutamate binding pocket of mGlu2 and mGlu3 receptors. It cannot be excluded that xanthurenic acid acts as a allosteric agonist (i.e., an allosteric compound endowed with intrinsic efficacy) of mGlu2/3 receptors, but this does not explain why inhibition of field excitatory post-synaptic potentials (fEPSP) by xanthurenic acid in hippocampal slices was insensitive to pharmacological blockade of mGlu2/3 receptors (Neale et al., 2013). Xanthurenic acid might interact with its own receptor (perhaps a not-yet identified G-protein coupled receptor), which may engage mGlu2/3 receptor signaling and might also signal *via* other mechanisms. Because of its putative action at mGlu2/3 receptors, xanthurenic acid might be involved in the pathophysiology and treatment of CNS disorders in which these receptors have been implicated, such as schizophrenia (see below), anxious-depressive disorders, chronic pain, drug addiction, and chronic neurodegenerative disorders (reviewed by Nicoletti et al., 2011; 2015; Conn et al., 2014; Walker et al., 2015; Bruno et al., 2016). Xanthurenic acid reduces pain sensitivity in the hot plate and tail flick models in rats (Heyliger et al., 1998), and changes in blood xanthurenic acid levels have been shown in patients affected by chronic migraine and cluster headache (Curto et al., 2016a,b). Because mGlu2 receptors negatively modulate nociceptive transmission (reviewed by Chiechio and Nicoletti, 2012) we predict an analgesic activity of xanthurenic acid in experimental animal models of chronic pain.

***3.3 Inhibition of the vesicular glutamate transporter***

Perhaps, the most likely explanation for some of the observed effects of xanthurenic acid (Neale et al., 2013) is that the compound targets other mechanisms regulating glutamatergic neurotransmission. Interestingly, xanthurenic acid inhibits vesicular glutamate transporters (VGLUTs) (Bartlett et.al. 1998), thereby preventing glutamate uptake into synaptic vesicles (see Neale et al., 2014). A series of structurally unrelated VGLUT inhibitors, such as Rose Bengal, Congo Red, and Chicago Sky Blue 6B, shares with xanthurenic acid the ability to depress fEPSPs at the Schaffer collateral-CA1 pyramidal cell synapses (Neale et al., 2014), and to reduce the amplitude of fEPSPs recorded in the dentate gyrus (Neale et al., 2013). Thus, it is possible that, at least in distinct CNS regions, xanthurenic acid inhibits glutamatergic transmission by blocking transport of L-glutamate into synaptic vesicles thereby ultimately reducing the synaptic release of L-glutamate. How this mechanism can be reconciled with the ability of kynurenic acid to activate mGlu2 and mGlu3 receptors is unclear.

***3.4 Xanthurenic acid and schizophrenia***

The mGlu2 receptor has been implicated in the pathophysiology of schizophrenia (Moghaddam and Adams, 1998; Aghajanian and Marek, 2000; Marek et al., 2000; Gonzales-Maeso et al., 2008; Moreno et al., 2016; Holloway et al., 2013; reviewed by Delille et al., 2013), and both mGlu2/3 orthosteric agonists and mGlu2 receptor PAMs show efficacy in experimental animal models that are predictive of antipsychotic activity (Fell et al., 2012; Hiyoshi et al., 2014; Walker and Conn, 2015). An exploratory analysis of clinical studies showed that pomeglumetad methionyl (the oral prodrug of the mGlu2/3 receptor agonist, LY404039) was effective in relieving both positive and negative symptoms in subgroups of patients affected by schizophrenia who were early in disease and had not been previously treated with atypical antipsychotics (Kinon et al., 2015). Xanthurenic acid displayed antipsychotic-like activity in mice challenged with [5R,10S]-[+]-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801) *via* the activation of mGlu2 receptors (Fazio et al., 2015). This action of xanturenic acid was seen at doses of 30-60 mg/kg, which are expected to increase brain xanthurenic acid concentrations to an extent sufficient for the activation of mGlu2 receptors (Fazio et al., 2015). Accordingly, basal xanthurenic acid concentrations in the rodent brain range from 0.4 and 1 M, and concentrations in the frontal cortex are increased by nearly 30 fold in response to peripheral injection of 50 mg/kg of xanthurenic acid (Gobaille et al., 2008). Interestingly, blood levels of xanthurenic acid were substantially reduced in a large cohort of patients affected by schizophrenia. This reduction persisted after months of treatment with antipsychotic drugs and was also observed in first-degree relatives of patients affected by schizophrenia (Fazio et al., 2015). Other kynurenine metabolites that lie downstream of KMO, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acd, and quinolinic acid were also reduced in the blood of patients affected of schizophrenia, as expected (Erhardt et al., 2001; Linderholm et al., 2012; Schwarcz et al., 2012; Kegel et al., 2014), but only xanthurenic acid and 3-hydroxyanthranilic acid were reduced in first-degree relatives of patients (Fazio et al., 2015). These findings suggest that (i) a reduction of xanthurenic acid production might contribute to the pathophysiology of schizophrenia by restraining the endogenous activation of mGlu2 receptors; and, (ii) blood levels of xanthurenic acid might represent a new peripheral biomarker that may allow the indentification of individuals at risk of developing schizophrenia. Such individuals might then be able to receive disease-modifying treatments in the early phases of the disorder. Blood levels of xanthurenic acid are also lower in patients affected by attention deficit and hyperactivity disorder (ADHD) (Aarsland et al., 2015) and cluster headache (Curto et al., 2016a), and are higher in patients affected by chronic migraine (Curto et al., 2016b). However, these changes are small and their biological significance is uncertain.

***3.5 Inhibition of tetrahydrobiopterin synthesis***

The discovery that xanthurenic acid is a potent inhibitor of sepiapterin reductase (Haruki et al., 2016) indicates that the function of xanthurenic acid in the CNS extends beyond the regulation of membrane transporters or neurotransmitter receptors. Sepiapterin reductase is the final enzyme in the *de novo* synthesis of tetrahydrobiopterin, the enzymatic cofactor of tyrosine hydroxylase, tryptophane hydroxylase, and nitric oxide synthase. This mechanism might limit the stimulation of tetrahydrobiopterin synthesis caused by pro-inflammatory cytokines (which also induce the kynurenine pathway), and might aso contribute to explain the psychiatric adverse effects of interferon treatment (Haruki et al., 2016). In addition, the expected – but not yet demonstrated - reduction in dopamine and serotonin synthesis that follows the inhibition of sepiapterin reductase might contribute to the putative antipsychotic-like activity of xanthurenic acid (see above). Inhibition of tetrahydrobiopterin synthesis by xanthurenic acid might also pave the way to the design of new drugs aimed at restraining dopamine or serotonin synthesis in psychiatric disorders such as drug addiction and schizophrenia.

**Conclusions**

It is becoming clear that many members of the kynurenine pathways can have complex effects in physiological systems both within the brain and in other parts of the body. In particular, both cinnabarinic acid and xanthurenic acid appear to be able to affect several diverse molecular targets and signaling systems that are only beginning to be uncovered. What is clear, however, is that these compounds can affect brain function and neurotransmission in a variety of ways, and that this may be altered under pathological conditions. Thus, future studies on the function of cinnabarinic acid and xanthurenic acid will no doubt result in better understanding of disease processes and may reveal new potential therapeutic targets in nervous system diseases.

**References**

Aarsland, T.I., Landaas, E.T., Hegvik, T.A., Ulvik, A., Halmøy, A., Ueland, P.M., Haavik, J., 2015. Serum concentrations of kynurenines in adult patients with attention-deficit hyperactivity disorder (ADHD): a case-control study. Behav Brain Funct. 11:36. doi: 10.1186/s12993-015-0080-x.

Aghajanian, G.K., Marek, G.J., 2000. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Brain Res Rev. 31:302-312. doi: 10.1016/S0165-0173(99)00046-6

Amori, L., Guidetti, P., Pellicciari, R., Kajii, Y., Schwarcz, R., 2009. On the relationship between the two branches of the kynurenine pathway in the rat brain in vivo. J Neurochem. 109:316-325. doi: 10.1111/j.1471-4159.2009.05893.x.

Baran, H., Staniek, K., Bertignol-Spörr, M., Attam, M., Kronsteiner, C., Kepplinger, B., 2016. Effects of Various Kynurenine Metabolites on Respiratory Parameters of Rat Brain, Liver and Heart Mitochondria. Int J Tryptophan Res. 9:17-29. doi: 10.4137/IJTR.S37973. eCollection 2016.

Bartlett, R.D., Esslinger, C.S., Thompson, C.M., Bridges, R. J., 1998. Substituted quinolines as inhibitors of l-glutamate transport into synaptic vesicles. Neuropharmacology 37:839-846. doi: 10.1016/S0028-3908(98)00080-X

Battaglia, G., Busceti, C.L., Molinaro, G., Biagioni, F., Traficante, A., Nicoletti, F., Bruno, V., 2006. Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. J Neurosci. 26:7222-7229. doi : 10.1523/JNEUROSCI.1595-06.2006

Bessede, A., Gargaro, M., Pallotta, MT.., Matino, D.., Servillo, G., Brunacci, C., Bicciato, S., Mazza, E.M., Macchiarulo, A., Vacca, C., Iannitti, R., Tissi, L., Volpi, C., Belladonna, M.L., Orabona, C., Bianchi, R., Lanz, T.V., Platten, M., Della Fazia, M.A., Piobbico, D., Zelante, T., Funakoshi, H., Nakamura, T., Gilot, D., Denison, M.S., Guillemin, G.J., DuHadaway, J.B., Prendergast, G.C., Metz, R., Geffard, M., Boon, L., Pirro, M., Iorio, A., Veyret, B., Romani, L., Grohmann, U., Fallarino, F., Puccetti, P., 2014. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. Nature. 511:184-190. doi: 10.1038/nature13323.

Bruno, V., Caraci, F., Copani, A., Matrisciano, F., Nicoletti, F., Battaglia, G., 2016. The impact of metabotropic glutamate receptors into active neurodegenerative processes: A "dark side" in the development of new symptomatic treatments for neurologic and psychiatric disorders. Neuropharmacology. 2016 pii: S0028-3908(16)30184-8. doi: 10.1016/j.neuropharm.2016.04.044.

Cain, C.D., Schroeder, F.C., Shankel, S.W., Mitchnick, M., Schmertzler, M., Bricker, N.S., 2007. Identification of xanthurenic acid 8-O-beta-D-glucoside and xanthurenic acid 8-O-sulfate as human natriuretic hormones. Proc Natl Acad Sci U S A. 104:17873-17878.

Chiechio, S., Nicoletti, F., 2012. Metabotropic glutamate receptors and the control of chronic pain. Curr Opin Pharmacol. 12:28-34. doi: 10.1016/j.coph.2011.10.010.

Christen, S., Southwell-Keely, P.T., Stocker, R., 1992. Oxidation of 3-hydroxyanthranilic acid to the phenoxazinone cinnabarinic acid by peroxyl radicals and by compound I of peroxidases or catalase. Biochemistry. 31:8090-8097. doi : 10.1021/bi00149a045

Conn, P.J., Lindsley, C.W., Meiler, J., Niswender, C.M., 2014. Opportunities and challenges in the discovery of allosteric modulators of GPCRs for treating CNS disorders. Nat Rev Drug Discov. 13:692-708. doi: 10.1038/nrd4308.

Copeland, C.S., Neale, S.A., Salt, T.E., 2013. Actions of Xanthurenic acid, a putative endogenous Group II metabotropic glutamate receptor agonist, on sensory transmission in the thalamus. Neuropharmacology. 66:133-142. doi: 10.1016/j.neuropharm.2012.03.009.

Curto, M., Lionetto, L., Negro, A., Capi, M., Perugino, F., Fazio, F., Giamberardino, M.A., Simmaco, M., Nicoletti, F., Martelletti, P., 2016a. Altered serum levels of kynurenine metabolites in patients affected by cluster headache. J Headache Pain. 17:27. doi: 10.1186/s10194-016-0620-2.

Curto, M., Lionetto, L., Negro, A., Capi, M., Fazio, F., Simmaco, M., Nicoletti, F., Martelletti, P., 2016b. Altered kynurenine pathway metabolites in the serum of patients affected by chronic migraine. J. Headache Pain., in the press. doi : 10.1186/s10194-016-0638-5

de Carvalho, L.P., Bochet, P., Rossier, J., 1996. The endogenous agonist quinolinic acid and the non endogenous homoquinolinic acid discriminate between NMDAR2 receptor subunits. Neurochem Int. 28:445-452.

Delille, H.K., Mezler, M., Marek, G.J., 2013. The two faces of the pharmacological interaction of mGlu2 and 5-HT2A - relevance of receptor heterocomplexes andinteraction through functional brain pathways. Neuropharmacology. 70:296-305. doi: 10.1016/j.neuropharm.2013.02.005.

Eggert, C., 1997. Laccase-catalyzed formation of cinnabarinic acid is responsible for antibacterial activity of Pycnoporus cinnabarinus. Microbiol Res. 152:315-318. doi: 10.1016/S0944-5013(97)80046-8

Esser, C., Rannug, A., Stockinger, B., 2009. The aryl hydrocarbon receptor in immunity. Trends Immunol. 30:447-454. doi: 10.1016/j.it.2009.06.005.

Erhardt, S., Blennow, K., Nordin, C., Skogh, E., Lindström, L.H., Engberg, G., 2001. Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia. Neurosci Lett. 313:96-98. doi: 10.1016/S0304-3940(01)02242-X

Fallarino, F., Volpi, C., Fazio, F., Notartomaso, S., Vacca, C., Busceti, C., Bicciato, S., Battaglia, G., Bruno, V., Puccetti, P., Fioretti, M.C., Nicoletti, F., Grohmann, U., Di Marco, R., 2010. Metabotropic glutamate receptor-4 modulates adaptive immunity and restrains neuroinflammation. Nat Med. 16:897-902. doi: 10.1038/nm.2183.

Fallarino, F., Romani, L., Puccetti, P., 2014. AhR: far more than an environmental sensor. Cell Cycle. 13:2645-2646. doi: 10.4161/15384101.2014.954219.

Fazio, F., Lionetto, L., Molinaro, G., Bertrand, H.O., Acher, F., Ngomba, R.T., Notartomaso, S., Curini, M., Rosati, O., Scarselli, P., Di Marco, R., Battaglia, G., Bruno, V., Simmaco, M., Pin, J.P., Nicoletti, F., Goudet, C., 2012. Cinnabarinic acid, an endogenous metabolite of the kynurenine pathway, activates type 4 metabotropic glutamate receptors. Mol Pharmacol. 81:643-656. doi: 10.1124/mol.111.074765.

Fazio, F., Zappulla, C., Notartomaso, S., Busceti, C., Bessede, A., Scarselli, P., Vacca, C., Gargaro, M., Volpi, C., Allegrucci, M., Lionetto, L., Simmaco, M., Belladonna, M.L., Nicoletti, F., Fallarino, F., 2014. Cinnabarinic acid, an endogenous agonist of type-4 metabotropic glutamate receptor, suppresses experimental autoimmune encephalomyelitis in mice. Neuropharmacology. 81:237-243. doi: 10.1016/j.neuropharm.2014.02.011.

Fazio, F., Lionetto, L., Curto, M., Iacovelli, L., Cavallari, M., Zappulla, C., Ulivieri, M., Napoletano, F., Capi, M., Corigliano, V., Scaccianoce, S., Caruso, A., Miele, J., De Fusco, A., Di Menna, L., Comparelli, A., De Carolis, A., Gradini, R., Nisticò, R., De Blasi, A., Girardi, P., Bruno, V., Battaglia, G., Nicoletti, F., Simmaco, M., 2015. Xanthurenic Acid Activates mGlu2/3 Metabotropic Glutamate Receptors and is a Potential Trait Marker for Schizophrenia. Sci Rep. 5:17799. doi: 10.1038/srep17799.

Fell, M.J., McKinzie, D.L., Monn, J.A., Svensson, K.A., 2012. Group II metabotropic glutamate receptor agonists and positive allosteric modulators as novel treatments for schizophrenia. Neuropharmacology. 62:1473-1483. doi: 10.1016/j.neuropharm.2011.06.007.

Fridén, M., Gupta, A., Antonsson, M., Bredberg, U., Hammarlund-Udenaes, M., 2007. In vitro methods for estimating unbound drug concentrations in the brain interstitial and intracellular fluids. Drug Metab Dispos. 35:1711-1719. doi: 10.1124/dmd.107.015222

Garcia, G.E., Wirtz, R.A., Barr, J.R., Woolfitt, A., Rosenberg, R., 1998. Xanthurenic acid induces gametogenesis in Plasmodium, the malaria parasite. J Biol Chem. 273:12003-12005. doi: 0.1074/jbc.273.20.12003

Gobaille, S., Kemmel, V., Brumaru, D., Dugave, C., Aunis, D., Maitre, M., 2008. Xanthurenic acid distribution, transport, accumulation and release in the rat brain. J Neurochem. 105:982-893. doi: 10.1111/j.1471-4159.2008.05219.x.

González-Maeso, J., Ang, R.L., Yuen, T., Chan, P., Weisstaub, N.V., López-Giménez, J.F., Zhou, M., Okawa, Y., Callado, L.F., Milligan, G., Gingrich, J.A., Filizola, M., Meana, J.J., Sealfon, S.C., 2008. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature. 452:93-97. doi: 10.1038/nature06612.

Goudet, C., Chapuy, E., Alloui, A., Acher, F., Pin, J.P., Eschalier, A., 2008. Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. Pain. 137:112-124. PubMed PMID: 17900808. doi: 10.1016/j.pain.2007.08.020.

Guidetti, P., Amori, L., Sapko, M.T., Okuno, E., Schwarcz, R., 2007. Mitochondrial aspartate aminotransferase: a third kynurenate-producing enzyme in the mammalian brain. J Neurochem. 102:103-111. doi: 10.1111/j.1471-4159.2007.04556.x

Guidetti, P., Hoffman, G.E., Melendez-Ferro, M., Albuquerque, E.X., Schwarcz, R., 2007. Astrocytic localization of kynurenine aminotransferase II in the rat brain visualized by immunocytochemistry. Glia. 55:78-92. doi: 10.1002/glia.20432

Guillemin, G.J., Smythe, G., Takikawa, O., Brew, B.J., 2005. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. Glia. 49:15-23. doi : 10.1002/glia.20090

Han, Q., Robinson, H., Cai, T., Tagle, D.A., Li, J., 2009. Biochemical and structural properties of mouse kynurenine aminotransferase III. Mol Cell Biol. 29:784-793. doi: 10.1128/MCB.01272-08.

Hanieh, H., 2014. Toward understanding the role of aryl hydrocarbon receptor in the immune system: current progress and future trends. Biomed Res Int. 2014:520763. doi: 10.1155/2014/520763.

Haruki, H., Hovius, R., Pedersen, M.G., Johnsson, K., 2016. Tetrahydrobiopterin Biosynthesis as a Potential Target of the Kynurenine Pathway Metabolite Xanthurenic Acid. J Biol Chem. 291:652-657. doi: 10.1074/jbc.C115.680488.

Heyliger, S.O., Goodman, C.B., Ngong, J.M., Soliman, K.F., 1998. The analgesic effects of tryptophan and its metabolites in the rat. Pharmacol Res. 38:243-250. doi : 10.1006/phrs.1998.0362

Hiyoshi, T., Marumo, T., Hikichi, H., Tomishima, Y., Urabe, H., Tamita, T., Iida, I., Yasuhara, A., Karasawa, J., Chaki, S., 2014. Neurophysiologic and antipsychotic profiles of TASP0433864, a novel positive allosteric modulator of metabotropic glutamate 2 receptor. J Pharmacol Exp Ther. 351:642-653. doi: 10.1124/jpet.114.218651.

Hoffman, A., Okun-Gurevich, M., Ovcharenko, E., Goltsman, I., Karram, T., Cain, C., Abassi, Z., Winaver, J., 2013. Renal effects of a novel endogenous natriuretic agent xanthurenic acid 8-o-β-d-glucoside in rats. Physiol Rep. 1:e00155. doi: 10.1002/phy2.155.

Holloway, T., Moreno, J.L., Umali, A., Rayannavar, V., Hodes, G.E., Russo, S.J., González-Maeso, J., 2013. Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: role of maternal immune system. J Neurosci. 33:1088-1098. doi: 10.1523/JNEUROSCI.2331-12.2013.

Joshi, A.D., Carter, D.E., Harper, T.A. Jr., Elferink, C.J., 2015. Aryl hydrocarbon receptor-dependent stanniocalcin 2 induction by cinnabarinic acid provides cytoprotection against endoplasmic reticulum and oxidative stress. J Pharmacol Exp Ther. 353:201-212. doi: 10.1124/jpet.114.222265.

Kawasaki, H., Chang, H.W., Tseng, H.C., Hsu, S.C., Yang, S.J., Hung, C.H., Zhou, Y., Huang, S.K., 2014. A tryptophan metabolite, kynurenine, promotes mast cell activation through aryl hydrocarbon receptor. Allergy. 69:445-452. doi: 10.1111/all.12346.

Kegel, M.E., Bhat, M., Skogh, E., Samuelsson, M., Lundberg, K., Dahl, M.L., Salgren, C., Schwieler, L., Engberg, G., Schuppe-Koistinen, I., Erhardt, S., 2014. Imbalanced kynurenine pathway in schizophrenia. Int J Tryptophan Res 7, 15-22. Doi : 10.4137/IJTR.S16800.

Kinon, B.J., Millen, B.A., Zhang, L., McKinzie, D.L., 2015. Exploratory analysis for a targeted patient population responsive to the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil in schizophrenia. Biol Psychiatry. 78:754-762. doi: 10.1016/j.biopsych.2015.03.016.

Linderholm, K.R., Skogh, E., Olsson, S.K., Dahl, M.L., Holtze, M., Engberg, G., Samuelsson, M., Erhardt, S., 2012. Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. Schizophr Bull. 38:426-432. doi: 10.1093/schbul/sbq086.

Lowe, M.M., Mold, J.E., Kanwar, B., Huang, Y., Louie, A., Pollastri, M.P., Wang, C., Patel, G., Franks, D.G., Schlezinger, J., Sherr, D.H., Silverstone, A.E., Hahn, M.E., McCune, J.M., 2014. Identification of cinnabarinic acid as a novel endogenous aryl hydrocarbon receptor ligand that drives IL-22 production. PLoS One. 9:e87877.doi: 10.1371/journal.pone.0087877.

Maaetoft-Udsen, K., Shimoda, L.M., Frøkiær, H., Turner, H., 2012. Aryl hydrocarbon receptor ligand effects in RBL2H3 cells. J Immunotoxicol. 9:327-337. doi:10.3109/1547691X.2012.661802.

Maj, M., Bruno, V., Dragic, Z., Yamamoto, R., Battaglia, G., Inderbitzin, W., Stoehr, N., Stein, T., Gasparini, F., Vranesic, I., Kuhn, R., Nicoletti, F., Flor, P.J., 2003. (-)-PHCCC, a positive allosteric modulator of mGluR4: characterization, mechanism of action, and neuroprotection. Neuropharmacology. 45:895-906. doi: 10.1016/S0028-3908(03)00271-5

Malina, H.Z., Martin, X.D., 1996. 3-hydroxykynurenine transamination leads to the formation of the fluorescent substances in human lenses. Eur J Ophthalmol. 6:250-256.

Malina, H.Z., Richter, C., Mehl, M., Hess, O.M., 2001. Pathological apoptosis by xanthurenic acid, a tryptophan metabolite: activation of cell caspases but not cytoskeleton breakdown. BMC Physiol. 1:7. doi: 10.1186/1472-6793-1-7

Malina, H.Z., Hess, O.M., 2004. Xanthurenic acid translocates proapoptotic Bcl-2 family proteins into mitochondria and impairs mitochondrial function. BMC Cell Biol. 5:14. doi: 10.1186/1471-2121-5-14

Marek, G.J., Wright, R.A., Schoepp, D.D., Monn, J.A., Aghajanian, G.K., 2000. Physiological antagonism between 5-hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex. J Pharmacol Exp Ther. 292:76-87.

Mezrich, J.D., Fechner, J.H., Zhang, X., Johnson, B.P., Burlingham, W.J., Bradfield, C.A., 2010. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol. 185:3190-3198. doi: 10.4049/jimmunol.0903670.

Moghaddam, B., Adams, B.W., 1998. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science. 281:1349-1352. doi: 10.1126/science.281.5381.1349

Moreno, J.L., Miranda-Azpiazu, P., García-Bea, A., Younkin, J., Cui, M., Kozlenkov, A., Ben-Ezra, A., Voloudakis, G., Fakira, A.K., Baki, L., Ge, Y., Georgakopoulos, A., Morón, J.A., Milligan, G., López-Giménez, J.F., Robakis, N.K., Logothetis, D.E., Meana, J.J., González-Maeso, J., 2016. Allosteric signaling through an mGlu2 and 5-HT2A heteromeric receptor complex and its potential contribution to schizophrenia. Sci Signal. 9:ra5. doi: 10.1126/scisignal.aab0467.

Neale, S.A., Copeland, C.S., Uebele, V.N., Thomson, F.J., Salt, T.E., 2013. Modulation of hippocampal synaptic transmission by the kynurenine pathway member xanthurenic acid and other VGLUT inhibitors. Neuropsychopharmacology. 38:1060-1067. doi: 10.1038/npp.2013.4.

Neale, S.A., Copeland, C.S., Salt, T.E., 2014. Effect of VGLUT inhibitors on glutamatergic synaptic transmission in the rodent hippocampus and prefrontal cortex. Neurochem Int. 73:159-165. doi: 10.1016/j.neuint.2013.10.001.

Nguyen, N.T., Kimura, A., Nakahama, T., Chinen, I., Masuda, K., Nohara, K., Fujii-Kuriyama, Y., Kishimoto, T., 2010. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. Proc Natl Acad Sci U S A. 107:19961-19966. doi: 10.1073/pnas.1014465107.

Nguyen, N.T., Nakahama, T., Le, D.H., Van Son, L., Chu, H.H., Kishimoto, T., 2014. Aryl hydrocarbon receptor and kynurenine: recent advances in autoimmune disease research. Front Immunol. 5:551. doi: 10.3389/fimmu.2014.00551. eCollection 2014.

Nickols, H.H., Conn, P.J., 2014. Development of allosteric modulators of GPCRs for treatment of CNS disorders. Neurobiol Dis. 61:55-71. doi: 10.1016/j.nbd.2013.09.013.

Nicoletti, F., Bockaert, J., Collingridge, G.L., Conn, P.J., Ferraguti, F., Schoepp, D.D., Wroblewski, J.T., Pin, J.P., 2011. Metabotropic glutamate receptors: from the workbench to the bedside. Neuropharmacology. 60:1017-1041. doi: 10.1016/j.neuropharm.2010.10.022.

Nicoletti, F., Bruno, V., Ngomba, R.T., Gradini, R., Battaglia, G., 2015. Metabotropic glutamate receptors as drug targets: what's new? Curr Opin Pharmacol. 20:89-94. doi: 10.1016/j.coph.2014.12.002.

Nuti, R., Gargaro, M., Matino, D., Dolciami, D., Grohmann, U., Puccetti, P., Fallarino, F., Macchiarulo, A., 2014. Ligand binding and functional selectivity of L-tryptophan metabolites at the mouse aryl hydrocarbon receptor (mAhR). J Chem Inf Model. 12:3373-3383. doi: 10.1021/ci5005459.

Ogawa, H., Nagamura, Y., Ishiguro, I., 1983. Cinnabarinic acid formation in Malpighian tubules of the silkworm, Bombyx mori. Participation of catalase in cinnabarinic acid formation in the presence of manganese ion. Hoppe Seylers Z Physiol Chem. 364:1059-1066.

Oxenkrug, G., Ratner, R., Summergrad, P., 2013. Kynurenines and vitamin B6: link between diabetes and depression. J Bioinform Diabetes. 1:1-10. doi: 10.14302/issn.2374-9431.jbd-13-218

Parsons, C.G., Danysz, W., Quack, G., Hartmann, S., Lorenz, B., Wollenburg, C., Baran, L., Przegalinski, E., Kostowski, W., Krzascik, P., Chizh, B., Headley, P.M., 1997. Novel systemically active antagonists of the glycine site of the N-methyl-D-aspartate receptor: electrophysiological, biochemical and behavioral characterization. J Pharmacol Exp Ther. 283:1264-1275.

Quintana, F.J., 2013. The aryl hydrocarbon receptor: a molecular pathway for the environmental control of the immune response. Immunology. 138:183-189. doi: 10.1111/imm.12046.

Rao, P.V., Vaidyanahan, C.S., 1966 Enzymic conversion of 3-hydroxyanthranilic acid into cinnabarinic acid. Partial purification and properties of ra-liver cinnabarinate synthase. Biochem J. 99:317-322.

Santi, M.R., Ikonomovic, S., Wroblewski, J.T., Grayson, D.R., 1994. Temporal and depolarization-induced changes in the absolute amounts of mRNAs encoding metabotropic glutamate receptors in cerebellar granule neurons in vitro. J Neurochem. 63:1207-1217. PubMed PMID: 7931274.

Sathyasaikumar, K.V., Tararina, M., Wu, H.Q., Schwarcz, R., 2014. Production of xanthurenic acid from 3-hydroxykynurenine in rat and human brain in vitro and in vivo. American Neuroscience Annual Meeting, Abs. 36, 23 (2014).

Schwarcz, R., Pellicciari, R., 2002. Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther. 303:1-10. doi: 10.1124/jpet.102.034439.

Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 13:465-477. doi: 10.1038/nrn3257.

Stephens, G.L., Wang, Q., Swerdlow, B., Bhat, G., Kolbeck, R., Fung, M., 2013. Kynurenine 3-monooxygenase mediates inhibition of Th17 differentiation via catabolism of endogenous aryl hydrocarbon receptor ligands. Eur J Immunol. 43:1727-1734. doi: 10.1002/eji.201242779.

Stevens, E.A., Mezrich, J.D., Bradfield, C.A., 2009. The aryl hydrocarbon receptor: a

perspective on potential roles in the immune system. Immunology. 127:299-311. doi: 10.1111/j.1365-2567.2009.03054.x.

Stone, T.W., Perkins, M.N., 1981. Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. Eur J Pharmacol. 72, 411–412.

Taleb, O., Maammar, M., Brumaru, D., Bourguignon, J.J., Schmitt, M., Klein, C., Kemmel, V., Maitre, M., Mensah-Nyagan, A.G., 2012. Xanthurenic acid binds to neuronal G-protein-coupled receptors that secondarily activate cationic channels in the cell line NCB-20. PLoS One. 7:e48553. doi: 10.1371/journal.pone.0048553.

Volpi, C., Fazio, F., Fallarino, F., 2012. Targeting metabotropic glutamate receptors in neuroimmune communication. Neuropharmacology. 63:501-506. doi: 10.1016/j.neuropharm.2012.05.024.

Volpi, C., Mondanelli, G., Pallotta, M.T., Vacca, C., Iacono, A., Gargaro, M., Albini, E., Bianchi, R., Belladonna, M.L., Celanire, S., Mordant, C., Heroux, M., Royer-Urios, I., Schneider, M., Vitte, P.A., Cacquevel, M., Galibert, L., Poli, S.M., Solari, A., Bicciato, S., Calvitti, M., Antognelli, C., Puccetti, P., Orabona, C., Fallarino, F., Grohmann, U., 2016 Allosteric modulation of metabotropic glutamate receptor 4 activates IDO1-dependent, immunoregulatory signaling in dendritic cells. Neuropharmacology. 102:59-71. doi: 10.1016/j.neuropharm.2015.10.036.

Walker, A.G., Conn, P.J., 2015. Group I and group II metabotropic glutamate receptor allosteric modulators as novel potential antipsychotics. Curr Opin Pharmacol. 20:40-45. doi: 10.1016/j.coph.2014.11.003.

Wonodi, I., Schwarcz, R., 2010. Cortical kynurenine pathway metabolism: a novel target for cognitive enhancement in Schizophrenia. Schizophr Bull. 36:211-218. doi: 10.1093/schbul/sbq002.

**Figure legend**

**Fig. 1** – The kynurenine pathway with highlight on cinnabarinic acid and xanthurenic acid.

IDO = indoleamine 2,3-dioxygenase ; TDO = tryptophan 2,3-dioxygenase ; KATs = kynurenine aminotransferases ; KMO = kynurenine monooxygenase ; 3-HAO = 3-hydroxyanthranilic acid 3,4-dioxygenase.

**Table 1 –** Putative targets and CNS functions of xanthurenic and cinnabarinic acids.

*Cinnabarinic acid Xanthurenic acid*

*Putative molecular targets* mGlu4 receptors Unidentified GPCR2,3

(orthosteric agonist)1

Ah receptor ligand4  mGlu2/3 receptors

(enhancing effect)5

vGLUT inhibition6,7,8

*Putative CNS functions* Inhibition of Inhibition of excitatory

Neuroinflammation9 synaptic transmission7,8,10

Neuroprotection1 Antipsychotic-like effect4

Analgesia11

Influence on monoaminergic

transmission due to inhibition

of BH4 biosynthesis12

Ah = aryl hydrocarbon receptor ; vGLUT = vesicular glutamate transporter ; BH4 = tetrahydrobiopterine. 1Fazio et al., 2012; 2Taleb et al., 2012; 3Gobaille et al., 2008; 4Lowe et al., 2014; 5Fazio et al., 2015; 6Bartlett et al., 1998; 7Neale et al., 2013; 8Neale et al., 2014; 9Fazio et al., 2014; 10Copeland et al., 2013; 11Heyliger et al., 1998; 12Haruki et al., 2016.