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Invited review

Cinnabarinic acid and xanthurenic acid: Two kynurenine metabolites that interact with metabotropic 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 function 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.

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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-hydroxyanthranilic 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., 2005; Guidetti et al., 2007a, 2007b; Amori et al., 2009; Han et al., 2009) Kynurenine monooxygenase (KMO), the enzyme that transforms L-kynurenine into 3-hydroxykynurenine, 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 (Fallarino 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, 1997), is generated from enzymatic and non-enzymatic oxidation of 3-hydroxyanthranilic acid (Rao and Vaidyanahan, 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 (Sathyasaikumar 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. Interestingly, 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

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