Neuropharmacology 113 (2017) 661–671

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The emerging pharmacology and function of GPR35 in the nervous system

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ARTICLE INFO

Article history:
Received 23 April 2015
Received in revised form
20 July 2015
Accepted 27 July 2015
Available online 29 July 2015

Keywords:
GPR35
Kynurenic acid
Zaprinast
Pain
CNS
Synaptic transmission

ABSTRACT

G protein-coupled receptor 35 (GPR35) is an orphan G protein-coupled receptor (GPCR) that can be activated by kynurenic acid at high micromolar concentrations. A previously unappreciated mechanism of action of GPR35 has emerged as a $G\alpha_{i/o}$-coupled inhibitor of synaptic transmission, a finding that has significant implications for the accepted role of kynurenic acid as a broad-spectrum antagonist of the NMDA, AMPA/kainite and α7 nicotinic receptors. In conjunction with previous findings that link agonism of GPR35 with significant reduction in nociceptive pain, GPR35 has emerged as a potential effector of regulation of mechanical sensitivity and analgesia of the Ret tyrosine kinase, and as a receptor involved in the transmission of anti-inflammatory effects of aspirin- potentially through affecting leucocyte rolling, adhesion and extravasation. Single nucleotide polymorphisms of GPR35 have linked this receptor to coronary artery calcification, inflammatory bowel disease and primary sclerosing cholangitis, while chromosomal aberrations of the 2q37.3 locus and altered copy number of GPR35 have been linked with autism, Albight's hereditary osteodystrophy-like syndrome, and congenital malformations, respectively. Herein, we present an update on both the pharmacology and potential function of GPR35, particularly pertaining to the nervous system. This review forms part of a special edition focussing on the role of lipid-sensing GPCRs in the nervous system.

This article is part of the Special Issue entitled 'Lipid Sensing G Protein-Coupled Receptors in the CNS'.

Contents

Abbreviations: AHO, Albright's hereditary osteodystrophy; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CNS, central nervous system; cGMP, cyclic guanosine 3′5′ monophosphate; DRG, dorsal root ganglion; EC_{50}, half-maximal effective concentration; GPR35, G protein-coupled receptor 35; GPCR, G protein-coupled receptor; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PKG, protein kinase G; RET, rearranged during transfection; SNP, single nucleotide polymorphism; TRPV1, transient receptor potential cation channel subfamily V member 1.

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http://dx.doi.org/10.1016/j.neuropharm.2015.07.035
0028-3908/

1. Introduction

GPR35 is a poorly characterised, 7-transmembrane domain, GPCR that transmits function via interaction with $G\alpha_{i/o}$, $G\alpha_{13}$, and β-arrestin (Fig. 1) (Milligan, 2011; Mackenzie et al., 2011; Divorty et al., 2015; Shore and Reggio, 2015). In terms of sequence similarity, GPR35 is related to the purinergic receptor LPA_4 (32%), the hydroxycarboxylic acid binding receptors HCA_2 and HCA_3 (30%), and the cannabinoid and lysophosphatidylinositol-binding GPR55 receptor (30%) (O'Dowd et al., 1998). As a consequence of the ligand-binding properties and shared sequence identity with GPR55, various groups have focussed on GPR35 as a putative lysophosphatidic acid-sensing GPCR (Oka et al., 2010; Zhao and Abood, 2013). This is of interest to further investigate experimentally, although at present it is difficult to draw any conclusions based on the original findings (Oka et al., 2010). Although certainly able to be activated by high concentrations of kynurenic acid, questions of which effects of this ligand, a well-studied metabolite of tryptophan, can be attributed to activation of GPR35 remain some of the major undefined issues in understanding the function of this receptor. This is vital to examine closely because kynurenic acid is clearly neuroactive and produces a broad range of effects in the central nervous system (CNS). However, many of these effects can be attributed to blockade of ionotropic receptors for the excitatory amino acid glutamate. Specific challenges in exploring the roles of GPR35 in the CNS relate to (a) the low potency of kynurenic acid at both rodent, and particularly the human, orthologues of the receptor, (b) that although many ligands with activity at GPR35 have been reported, the vast majority of these display modest potency and are known to also have a range of non-GPR35 mediated effects and, (c) although antagonists from two distinct chemical classes have been identified, at least in transfected cell systems these appear to display exquisite selectivity for human GPR35 and lack significant affinity at either mouse or rat GPR35 (Jenkins et al., 2012). Moreover, although a line of GPR35 knock-out mice has been generated and reported on (Min et al., 2010), these have not been employed widely and, currently, no information on the elimination of expression of GPR35 on effects of kynurenic acid in cells or tissue from the CNS has been released into the public domain. Each of these issues will be considered within the current review range of effects in the central nervous system (CNS). However, many of these effects can be attributed to blockade of ionotropic receptors for the excitatory amino acid glutamate. Specific challenges in exploring the roles of GPR35 in the CNS relate to (a) the low potency of kynurenic acid at both rodent, and particularly the human, orthologues of the receptor, (b) that although many ligands with activity at GPR35 have been reported, the vast majority of these display modest potency and are known to also have a range of non-GPR35 mediated effects and, (c) although antagonists from two distinct chemical classes have been identified, at least in transfected cell systems these appear to display exquisite selectivity for human GPR35 and lack significant affinity at either mouse or rat GPR35 (Jenkins et al., 2012). Moreover, although a line of GPR35 knock-out mice has been generated and reported on (Min et al., 2010), these have not been employed widely and, currently, no information on the elimination of expression of GPR35 on effects of kynurenic acid in cells or tissue from the CNS has been released into the public domain. Each of these issues will be considered within the current review.

2. Pharmacology

2.1. Putative endogenous agonists of GPR35

GPR35 retains “orphan” GPCR status despite being able to be stimulated by high concentrations of a number of endogenously produced small molecules, including kynurenic acid, 2-oleoyl lysophosphatidic acid, DHICA (5,6-dihydroxyindole-2-carboxylic acid), reverse T3 (3,3,5-triiodothyronine), cGMP (cyclic guanosine 3′5′ monophosphate), (Wang et al., 2006; Oka et al., 2010; Deng et al., 2012a; Southern et al., 2013), and, most recently, more modest levels of the chemokine CXCL17 (Maravillas-Montero et al., 2014). This reflects that reported estimates of ligand concentration in man, under normal physiological conditions at least, are less than those required to modulate the activity of the receptor substantially (e.g. kynurenic acid, DHICA, reverse T3 and cGMP (Divorty et al., 2015)), or have been described in single publications that have not yet been verified by independent sources (e.g. CXCL17 and derivatives of lysophosphatidic acid). The linkage of endogenously produced molecules with GPR35 activation is further complicated by marked differences in concentrations required to activate species homologues of this receptor (Milligan, 2011). This has led to the suggestion that kynurenic acid could feasibly be an/the endogenous ligand of rat but not human GPR35 (Mackenzie et al., 2011). A further point to note is that additional studies are required to verify the finding that CXCL17 is an/the endogenous ligand of GPR35 before the suggested systematic nomenclature of “CXCR8” (Maravillas-Montero et al., 2014) is agreed upon. Although this terminology has already appeared in subsequent literature (Shore and Reggio, 2015), definition of receptor de-orphanisation and adoption of a new nomenclature requires acceptance by the relevant subcommittee of the International Union of Basic and Clinical Pharmacology (IUPHAR). This has not yet occurred.

2.2. Synthetic agonists of GPR35

Since there is no consensus on the endogenous ligand(s) of this receptor, a large and concerted effort in both academic (Jenkins et al., 2010; Zhao et al., 2010; Funke et al., 2013; Thimm et al., 2013) and industrial (Taniguchi et al., 2006, 2008; Yang et al., 2010, 2012; Deng et al., 2011a, 2011b, 2012a) sectors; in addition to working collaborations between the two (Neetoo-Isseljee et al., 2013; Mackenzie et al., 2014), has resulted in reports of a wide range of novel and previously reported small molecule agonists from both distinct, and overlapping, chemical series that are able to activate GPR35. Such ligands include zaprinast, pamoic acid, YE-120, YE-210, tyrphostin-51, compound 1/TC-G 1001, PSB-13253, lodoxamide, bufrolin, amlexanox, furosemide and cromolyn