Neurobiology of Disease xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Neurobiology of Disease

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

Review

Development of allosteric modulators of GPCRs for treatment of CNS disorders

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ARTICLE INFO

Article history:
Received 25 July 2013
Revised 13 September 2013
Accepted 17 September 2013
Available online xxxx

Keywords:
Allosteric modulator
CNS
Drug discovery
GPCR
Metabotropic glutamate receptor
Muscarinic acetylcholine receptor

ABSTRACT

The discovery of allosteric modulators of G protein-coupled receptors (GPCRs) provides a promising new strategy with potential for developing novel treatments for a variety of central nervous system (CNS) disorders. Traditional drug discovery efforts targeting GPCRs have focused on developing ligands for orthosteric sites which bind endogenous ligands. Allosteric modulators target a site separate from the orthosteric site to modulate receptor function. These allosteric agents can either potentiate (positive allosteric modulator, PAM) or inhibit (negative allosteric modulator, NAM) the receptor response and often provide much greater subtype selectivity than orthosteric ligands do for the same receptors. Experimental evidence has revealed more nuanced pharmacological modes of action of allosteric modulators, with some PAMs showing allosteric agonism in combination with positive allosteric modulation in response to endogenous ligand (ago-potentiators) as well as "bitopic" ligands that interact with both the allosteric and orthosteric sites. Drugs targeting the allosteric site allow for increased drug selectivity and potentially decreased adverse side effects. Promising evidence has demonstrated potential utility of a number of allosteric modulators of GPCRs in multiple CNS disorders, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, as well as psychiatric or neurobehavioral diseases such as anxiety, schizophrenia, and addiction.

Contents

Abbreviations: 5MPEP, 5-methyl-6-(phenylethynyl)-pyridine; 6-OHDA, 6-hydroxydopamine; 7TMR, seven transmembrane receptor; 77-LH-28-1, 1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1H)-quinolinone; AC-42, 4-n-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine; AChE, acetylcholinesterase; ACPT-1, (1S,3R,4S)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid; AD, Alzheimer's disease; ADX71743, (+)-6-(2,4-dimethylphenyl)-2-ethyl-6,7-dihydrobenzo[d]oxazol-4(5H)-one; AFQ056, (3a*S*,5*S*,7a*R*)-methyl 5-hydroxy-5-(*m*-tolylethynyl) octahydro-1*H*-indole-1-carboxylate; APP, amyloid precursor protein; BINA, potassium 30-([(2-cyclopentyl-6-7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5yl)oxy]methyl)biphenyl l-4-carboxylate; BQCA, benzylquinolone carboxylic acid; CDPPB, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide; CFMMC, 3-cyclohexyl-5-fluoro-6-methyl-7-(2-morpholin-4-ylethoxy)-4H-chromen-4-one; CNS, central nervous system; CPPHA, *N*-[4-chloro-2[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl]-2-hydrobenzamide; CTEP, 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1*H*imidazol-4-yl)ethynyl)pyridine; DA, dopamine; DFB, [(3-fluorophenyl)methylene]hydrazone-3-fluorobenzaldehyde; DHPG, dihydroxyphenylglycine; ERK1/2, extracellular signal-regulated kinase 1/2; FMRP, fragile X mental retardation protein; FTIDC, 4-[1-(2-fluoropyridin-3-yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methyl-3,6-dihydropyridine-1(2H)-carboxamide; FXS, Fragile X syndrome; GABA, γ-aminobutyric acid; JNJ16259685, (3,4-dihydro-2H-pyrano[2,3]b quinolin-7-yl)(cis-4-methoxycyclohexyl) methanone; L-AP4, L-(+)-2-amino-4-phosphonobutyric acid; L-DOPA, L-3,4-dihydroxyphenylalanine; Lu AF21934, (1*S*,2*S*)-N^1-(3,4-dichlorophenyl)cyclohexane-1,2-dicarboxamide; Lu AF32615, 4-((*E*)-styryl)-pyrimidin-2-ylamine; mGlu, metabotropic glutamate receptor; M-5MPEP, 2-(2-(3-methoxyphenyl)ethynyl)-5-methylpyridine; MMPIP, 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-c]pyridin-4(5H)-one; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MTEP, 3[(2-methyl-1,3-thiazol-4-yl)ethylnyl]pyridine; NAM, negative allosteric modulator; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PCP, phencyclidine; PD, Parkinson's disease; PD-LID, Parkinson's disease levodopa-induced dyskinesia; PET, positron emission tomography; PHCCC, *N*-phenyl-7-(hydroxylimino)cyclopropa[*b*]chromen-1a-carboxamide; PQCA, (1-(4-cyano-4-(pyridine-2-yl)piperidine-1-yl)methyl-4-oxo-4 H-quinolizine-3-carboxylic acid); SAM, silent allosteric modulator; SIB-1757, 6-methyl-2-(phenylazo)-3-pyridinol; SIB-1893, 2-methyl-6-(2-phenylethenyl)pyridine; TBPB, 1-(1′-(2-methylbenzyl)-1,4′-bipiperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

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Available online on ScienceDirect (www.sciencedirect.com).

0969-9961/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.nbd.2013.09.013

Introduction

There is an urgent need for the development of new therapeutic agents for the treatment of debilitating CNS diseases, which affect millions of people worldwide. While the discovery and development of new therapeutic agents are challenging for all therapeutic areas, CNS drug discovery efforts have been especially challenging and have a very high attrition rate (Kola and Landis, 2004). The GPCRs have been among the most fruitful targets for developing drugs for the treatment of CNS disorders, as well as range of other human disease states. Many current clinical therapeutic agents act by targeting this important receptor class and downstream signaling pathways (Allen and Roth, 2011; Fang et al., 2003; Melancon et al., 2012). However, some major subfamilies of GPCRs have proven intractable in drug discovery efforts because of a difficulty in achieving high subtype selectivity and drug-like properties, including high CNS exposure, that are critical for advancing novel agents for the treatment of neurological and psychiatric disorders. Historically, drug discovery efforts targeting GPCRs have focused on the development of traditional agonists and antagonists that interact with the orthosteric neurotransmitter binding site to either mimic or block the action of the endogenous neurotransmitter or agonist. While this has been fruitful, there are many instances where the high conservation of the orthosteric binding site across related receptors prevents the development of subtype selective agents. Also, developing drug candidates based on the chemical scaffolds of the endogenous ligand may raise challenges in establishing appropriate profiles in terms of pharmacokinetic properties or brain exposure.

In recent years, advances in the development of allosteric modulators of GPCRs have emerged as a promising new approach for developing therapeutic agents that may be useful for the treatment of CNS disorders. Allosteric modulators of GPCRs bind to sites that are separate from the orthosteric binding site of the endogenous ligand and are often less highly conserved than the orthosteric site (Conn et al., 2009a). For some GPCRs, this has allowed optimization of allosteric modulators that achieve much greater subtype selectivity than is possible with traditional orthosteric ligands. In addition, allosteric modulators have other potential advantages, including ability to develop agents that have functional selectivity, allowing for potential targeting of select downstream signaling pathways, and a greater diversity of chemical scaffolds that can facilitate efforts to optimize pharmacokinetic and other drug-like properties of potential drug candidates. The surge in the development of allosteric agents has revealed a varied repertoire of drug activities, including PAMs and NAMs as well as agents with combined allosteric agonist and PAM activity and neutral ligands, termed silent allosteric modulators (SAMs) that bind to the allosteric site but do not potentiate or inhibit responses to the endogenous agonist (see Conn et al., 2009a; Melancon et al., 2012; Niswender and Conn, 2010 for reviews). In addition, allosteric agonists with a bitopic binding mode (binds to both the allosteric site and the orthosteric site) have been identified (Digby et al., 2012a; Lebon et al., 2009; Spalding et al., 2002). These varied modes of action provide tools for experimental investigation into GPCR structure and function. To date, there is a wide variety of allosteric modulators that are showing promise for potential treatment of CNS diseases (Conn et al., 2009d). Among these, some of the most advanced and well understood include allosteric modulators of the metabotropic glutamate (mGlu) receptors and the muscarinic acetylcholine receptors (mAChRs). For instance, allosteric modulators of specific subtypes of mGlu receptors have potential utility in the treatment of schizophrenia, autistic spectrum disorders, and Parkinson's disease (Morin et al., 2013b). Positive allosteric modulators of the M_1 and M_4 muscarinic receptors show promising applications in both Alzheimer's disease and schizophrenia. This is an exciting time in CNS drug discovery with several allosteric modulator candidates moving from preclinical models into clinical development.

Allosteric modulators of GPCRs

GPCRs, also called seven transmembrane spanning receptors (7TMRs), represent the largest family of cell surface receptors and are the targets of intense drug discovery efforts. While a number of available drugs on the market target GPCR signaling pathways, overall less than 20% of GPCRs are targeted (Allen and Roth, 2011). Ubiquitous receptors, these seven transmembrane-spanning proteins transduce extracellular signals for ligands as diverse as ions, photons of light, odorants and peptides into intracellular signaling cascades. Over 800 human GPCRs have been identified to date with five major families (and multiple subfamilies) based on their amino acid sequences (Katritch et al., 2013). Despite intense drug discovery and development efforts, clinically useful drugs do not exist for the large majority of these receptors. As noted above, the orthosteric binding site within GPCR subfamilies is often highly conserved, making the development of subtype specific ligands difficult. Of the orthosteric ligands developed, many of those with the highest subtype selectivity are antagonists.

Discovery and optimization of novel highly selective allosteric modulators of GPCRs have opened exciting new opportunities for the development of highly selective drug candidates for specific GPCR subtypes that were intractable using traditional approaches. While the major advances in the discovery of allosteric modulators of GPCRs have only occurred over the past decade, the principle of targeting allosteric sites on neurotransmitter receptors that act as ligand-gated ion channels has a long history and has been highly successful in developing agents for the treatment of CNS disorders (Melancon et al., 2012). The classic example of an allosteric modulator is the benzodiazepine class, which are positive allosteric modulators at the $GABA_A$ receptors (Mohler et al., 2002). These agents provide effective treatment of anxiety, sleep, and seizure disorders without inducing the adverse side effects

Please cite this article as: Nickols, H.H., Conn, P.J., Development of allosteric modulators of GPCRs for treatment of CNS disorders, Neurobiol. Dis. (2013), http://dx.doi.org/10.1016/j.nbd.2013.09.013