GPCRs of Diverse Physiologic and Pathologic Effects with Fingerprints in COVID-19[†]

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Abstract: G-protein-coupled receptors (GPCR) belong to a large family of molecules eliciting different responses to a variety of signaling molecules. These receptors participate in various physiological functions such as metabolism, growth, immune responses, inflammation, vision, taste, olfaction, and neurotransmission as well as in pathologic responses including chronic inflammatory and vascular diseases. Receptors contributing to the biological responses of the renin–angiotensin system (RAS) are members of the GPCR family. COVID-19-induced inflammatory cascade has been attributed to acute ACE2 downregulation and imbalance of proinflammatory ACE/AngII/AT1R and anti-inflammatory ACE2/angiotensin (1–7)/Mas axes in favor of the former. Some of the receptors contributing to activities of proteins in RAS, including AT1R, AT2R, Mas receptors, and Mas-related GPCR-member D receptor are members of the GPCR family. It is notable that these receptors induce their effects both through G-protein and β -arrestin pathways; the former exerts temporary and the latter more sustained effects. In addition to the imbalance of GPCR responses contributing to RAS activities, it has been suggested that SARS-CoV2 pathogenesis might be attributed to the activation of GPCRs or modulating G proteins involved in the adenosine–CFTR regulation system and epithelial Na-channel function. This article includes a minireview of the physiological functions of GPCRs and their contribution to COVID-19.

Keywords: ACE2; Ang II; AT1R; AT2R; Angiotensin (1–7); ARDS; COVID-19; CFTR; ENaC; $G\alpha$; $G\beta\gamma$; GPCR; Mas receptor; MrgD receptor; PKC; renin-angiotensin system (RAS); SARS-CoV2

1. Introduction

Cell-signaling, an adaptive strategy of cells in interaction with the environment, involves cellular chemical interaction to provoke appropriate responses to increase their survival. Cells release signaling molecules to bind to the receptors expressed in and on themselves or on neighboring or remote cells to initiate, integrate, or coordinate their activities [1]. Receptors are of different families. G-protein-coupled receptors (GPCR), as a large family of proteins encoded in the mammalian genome, contribute to many physiologic functions including vision, olfaction, taste, neurotransmission, metabolism, cell differentiation, immunity, inflammation, and prohormone signaling and, if dysregulated, can lead to several pathologic processes including hypersensitivity to angiotensin II and

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inflammatory and vascular diseases [2–4]. These receptors share a common counter-clockwise bundle structure composed of a single polypeptide with an extracellular N-terminus, an intracellular C-terminus and a hydrophobic seven-transmembrane domain (TM) connected by three intracellular and three extracellular loops [4,5] (Figure 1).

Figure 1. A typical beta2 adrenergic G protein coupled protein (GPCR) coupled to Gs family of $G\alpha$ protein.

However, despite this common structure, the functional diversity and heterogeneous amino acid sequence of GPCRs make it difficult to propose a comprehensive classification method of this receptor superfamily [6]. Once, GPCRs were classified based on ligand specificity or chemical properties of their primary residues, independent of the amino acid sequence [7,8]. Later, both characterization of sequence alignment and motifs as well as computational methods using machine learning algorithms such as those obtained from support vector machines (SVMs) associated with statistical models provided a rather

robust way of prediction and classification of GPCRs [9,10]. Focusing on integration of the structure, amino acid sequence, and function of this receptor superfamily, the GPCR database (GPCRdb), a molecular class-specific information system, has made possible a reliable approach to classifying GPCRs. This database encompasses all human non-olfactory GPCRs along with G proteins, human β -arrestins and more than 28,000 orthologs updated continuously [11,12]. Recently, a novel GPCR data base, the GPCR ensemble database (GPCREnDB) containing 3129 confirmed GPCR and 3575 non-GPCR sequences has been introduced [13]. Based on sequence homology and functional similarity, the most widely used A–F classification of the GPCR family and subfamily in both vertebrates and invertebrates was suggested—Class A, rhodopsin-like; Class B1, secretin-like; Class B2, adhesion receptors; Class C, metabotropic glutamate receptors; Class D, pheromone receptors; Class E, cAMP receptors; and Class F, frizzled smoothed family [4,14,15]. Vertebrates do not possess D and E classes. Alternatively, GRAFS classification phylogenetically groups GPCRs into five families—glutamate (class C), rhodopsin (class A), adhesion (class B2), frizzled (class F), and secretin (class B1) [16–18]. These groups are hierarchically further divided into subfamilies, sub-subfamilies, and types, based on their specific ligands and function [12,19,20]. As phylogenetic classification fails to fully support receptor family structure in diverse species due to continuous novel genome characterization, a modified classification method, the level-based system, has been suggested [21].

Upon binding with agonistic ligands, GPCRs adopt a proton-transport-dependent conformational change and activate cytoplasmic heterotrimeric G proteins (containing $G\alpha/G\beta\gamma$ subunits) through dissociation or conformational rearrangement (rotation of 130°) of $G\alpha$ from the $G\beta\gamma$ complex triggered by exchange of GTP for GDP in the $G\alpha$ subunit [22–25]. Human cells contain 16 $G\alpha$, 5 $G\beta$, and 13 $G\gamma$ subunit combinations which yield a great number of heterotrimeric G proteins [15]. Depending on the family of $G\alpha$ subunit activated by GPCR, a second messenger including cAMP, inositol phosphates (IP), Ca^{2+} , and diacylglycerol (DAG) is induced which stimulates some intracellular pathways such as MAPK, PI3K-Akt, and Ras and Rho GTPases [26,27].

Based on the structure and function of the $G\alpha$ subunit, G proteins are divided into four main families— $G\alpha_s$, $G\alpha_{o/i}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$ [28]. The $G\alpha_s$ family consists of $G\alpha_s$ and $G\alpha_{olf}$, while the $G\alpha_{o/i}$ family consists of $G\alpha_{i1}$, $G\alpha_{i2}$, $G\alpha_{i3}$, $G\alpha_o$, $G\alpha_{t1}$, $G\alpha_{t2}$, $G\alpha_{t3}$, and $G\alpha$. The $G\alpha_{q/11}$ family encompasses $G\alpha_q$, $G\alpha_{11}$, $G\alpha_{14}$, and $G\alpha_{16}$, and the $G\alpha_{12/13}$ family comprises $G\alpha_{12}$ and $G\alpha_{13}$ [29]. The $G\alpha_s$ family contributes to activation of adenylyl cyclase, $G\alpha_{o/i}$ inhibits adenylyl cyclase and induces ion transport, $G\alpha_{q/11}$ activates phospholipase C (PLC), and $G\alpha_{12/13}$ is involved in the Na^+/H^+ exchange pathway [30].

It is of paramount importance that ligand–GPCR interaction is not a simple on/off switch. In fact, GPCR stimulation, depending on the energy transferred between ligand and G protein, is a complex phenomenon and may lead to multiple responses so that specific ligands may induce different pathways. Ligands may function as full, partial, or inverse agonist, or a neutral antagonist [31]. Even GPCR signaling system has recently been shown to be capable of responding to different concentrations of the cognate ligand with distinct responses [32].

After propagation of the response, hydrolysis of GTP to GDP by the GTPase intrinsic activity of the $G\alpha$ subunit ends G-protein signaling transduction. GTPase-activating proteins (GAPs) and regulators of G-protein signaling (RGS) accelerate this reaction. This results in recreation of a $G\alpha/G\beta\gamma$ complex for the next signal transduction [32]. Alternatively, after activation of GPCRs, phosphorylation of serine and threonine residues on the C-terminal end or third intracellular loop of the receptors by GPCR kinases (GRK) creates a binding site for β -arrestins. Binding with β -arrestins shuts down G-dependent signaling cascades through desensitization of the receptor to the next ligand or internalization of the receptor and promotion of multiple G-independent pathways by inducing different protein-kinase-dependent pathways [33–35]. For instance, internalization of the complex of ligand activated GPCRs and β -arrestin promotes prolonged MAPK signaling predominantly in the cytoplasm and independent of G-protein signaling [33].

Intriguingly, GPCRs can also be found within the cells residing on membranous organelles such as endoplasmic reticulum, Golgi apparatus, and endosomes with the ability to translocate to the nucleus. After internalization, AT1R, apelin, and bradykinin2 receptors as well as receptors for chemokines may use canonical nuclear localization signals (NLSs) recognized by the karyopherin superfamily for nuclear import [36,37].

2. COVID-19 and GPCRs

SARS-CoV2, one of the members of β -family of coronaviruses and the cause of COVID-19 has resulted in a pandemic with a huge social economical and healthcare burden [38]. The resulting insult leads to acute inflammation in the lungs similar to the pathology seen in acute respiratory distress syndrome. It is worth mentioning that SARS-CoV2, like SARS-CoV, evades the immune system [39,40]. Accordingly, failure to activate a well-orchestrated effective innate immunity leads to eruption of an abortive adaptive immunity with the inability to resolve the pathology and clearance of infected cells. This results in sequential uninterrupted production of inflammatory mediators and eventually, a cytokine storm [41,42].

GPCRs contribute to inflammation with their presence as receptors for chemoattractants and chemokines on the cells such as polymorphonuclears, monocytes, macrophages, and endothelial cells and by mediating the production of cytokines and other inflammatory molecules [43]. Based on a great amount of data, the elicited profound inflammatory responses in COVID-19 has been attributed to an imbalance in the local renin angiotensin system (RAS) [44]. SARS-CoV2 on entry the host cell uses ACE2 as its receptor which is itself a transmembrane carboxy-monopeptidase of RAS converting Ang II to angiotensin (1–7) [45,46]. Acute downregulation of ACE2 resulting from internalization of virus–ACE2 complexes to the infected cells, as may occur in showering of a tremendous number of SARS-CoV2 virions to the lower airways, leads to an acute imbalance of the two major arms of local RAS, the ACE/Ang II/AT1R and ACE2/angiotensin (1–7)/Mas receptor pathways, in favor of the former [47]. ACE/Ang II/AT1R signaling elicits pro-inflammatory, pro-thrombotic, pro-apoptotic, and oxidative responses while the ACE2/angiotensin (1–7)/Mas receptor pathway predominantly provokes anti-inflammatory, anti-thrombotic, and anti-apoptotic effects [48]. Ang II-mediated AT1R stimulation upregulates phosphorylation of Yes-associated protein (YAP) and activates macrophages and their adhesion to endothelial cells [49]. Intriguingly, AT1R, AT2R, and the Mas receptor are members of GPCR family [50–53] although AT2R may also promote ERK1/2 and nitric oxide synthase (NOS) through a GPCR- or arrestin-independent pathway [54]. AngII activation of AT1R induces inflammatory responses through various G proteins— $G_{\alpha_{o/i}}$, $G_{\alpha_{q/11}}$, and $G_{\alpha_{12/13}}$ [55]. G_{α_q} activation of PLC produces DAG and IP3. The latter promotes intracellular calcium mobilization which, in collaboration with DAG activates various protein kinase C involved in inducing innate and adaptive immunity components such as TL4, inducible NOS, and NF- κ B signaling as well as gene expression and release of an array of cytokines such as TNF- α in tissues including the lungs [55–58]. Furthermore, PKC contributes to oxidative stress as a mediator of NADPH-oxidase activation and plays a role in neutrophil extracellular-trap (NET) formation [59]. In addition, calcium influx leads to disassembly of intercellular adhesion and cell retraction in endothelial cells resulting in increased permeability of the vascular wall [60]. Similar to other GPCRs, AT1R, after being complexed with β -arrestin, is internalized and the signaling transduction ends. The receptor may either be recycled to the cell membrane or degraded intracellularly. Alternatively, AT1R activation induces β -arrestin regulation of various MAPK-cascade members including p38MAPK, ERK, and JNK [55]. Angiotensin (1–7) promotes anti-inflammatory effects both via Mas/GPCR receptors and the AT1R/GPCR-mediated β -arrestin pathway [61]. It is implicated that in COVID-19 sustained imbalance of the two GPCR-mediated pathways in local RAS with predominance of AT1R over Mas-receptor signaling may ultimately result in severe inflammatory responses and multiple organ failure with utmost similarity to macrophage activation syndrome or other kinds of cytokine storms [47,62].

To make it more complex, homomerization and heteromerization of GPCRs, recognized as a constitutive property of this receptor superfamily that modulates receptor-evoked responses [63–65], may affect the adverse outcome of the hypothetical imbalance of counteracting arms of RAS in the pathogenesis of COVID-19. Receptor homomerization and heteromerization may lead to altered ligand binding, plasma-membrane diffusion, receptor endocytosis, and signaling transduction which may potentiate or attenuate pathobiological changes in the diseases [43,66]. For example, AT1R-bradykinin type 2 receptor (AT1R-B2R) complex may induce hypersensitivity to Ang II, while AT1R-AT2R complex reduces responses elicited by AT1R. Moreover, Ang (1–7)/Mas receptor in heteromerization with AT1R reduces the functional activities of the latter [67].

SARS-CoV2 has been suggested to induce lung edema through the cystic fibrosis transmembrane-conductance regulator (CFTR) system and epithelial Na⁺ channel (ENaC) function [68,69]. CFTR predominantly regulated by cAMP/PKA, the second messenger of the GPCR system, inhibits ENaC function, is yet to be elucidated meticulously [70,71]. ENaC as a member of voltage-independent Na⁺-selective ENaC/DEG ion channels is involved in airway and alveolar-space fluid clearance by epithelial and alveolar cells of the lungs [72,73]. SARS-CoV and some other viruses infecting the lungs, including the influenza virus, have been shown to decrease the activity of ENaC through activation of phosphokinase C (PKC) [74,75]. PKC, upregulated by extracellular purinergic receptors, which are themselves of or intricately interact with the GPCR family, may exert negative influence on ENaC cell-membrane trafficking and expression [76,77]. In addition, GPCR affects ENaC activity through phosphatidylinositol 4,5-bisphosphate (PI4,5-P) [78].

Furthermore, complement 5a receptor1 (C5aR1), a member of the GPCR family, has recently been proposed to be involved in COVID-19 pathogenesis [79]. GPCR4, which regulates vascular permeability and leukocyte recruitment, has also been hypothesized to play a part in SARS-CoV2 infection [80].

3. Conclusions and Future Perspectives

GPCRs, as a large family of receptors in cell-signaling systems, contribute to a huge number of broad physiologic and pathologic responses. The effects of these receptors can be traced in a vast array of infections. As for the complex pathogenesis of SARS-CoV2 infection which requires the contribution of GPCRs and the sustained responses that these receptors may exert at intracellular scale, they might be a good target for production of drugs that could restrict this infection and improve the long-term sequelae of the disease through restoring cell homeostasis.

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Abbreviations

ACE	angiotensin converting enzyme
ACE2	angiotensin converting enzyme2
Ang II	angiotensin II
AT1R	type I angiotensin II receptor
AT2R	type II angiotensin II receptor
CFTR	cystic fibrosis transmembrane conductance regulator

ENaC	epithelial Na Channel
GPCR	G-protein-coupled receptor
NOS	nitric oxide synthase
RAS	renin angiotensin system

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