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A Latin American Perspective on G Protein–Coupled Receptors

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ABSTRACT

G protein–coupled receptors are sensors that interact with a large variety of elements, including photons, ions, and large proteins. Not surprisingly, these receptors participate in the numerous normal physiologic processes that we refer to as health and in its perturbations that constitute disease. It has been estimated that a large percentage of drugs currently used in therapeutics target these proteins, and this percentage is larger when illegal drugs are included. The state of the art in this field can be defined with the oxymoron "constant change," and enormous progress has been made in recent years. A group of scientists working in Latin America were invited to contribute minireviews for this special section to present some of the work performed in this geographical region and foster further international collaboration.

Perspective

G protein–coupled receptors (GPCRs) constitute one of the main protein families through which cells sense the external environment (e.g., light, odors, tastants, or mating factors [yeast]) and the milieu intérieur of multicellular organisms (e.g., hormones, neurotransmitters, autacoids, and other mediators). These receptors made their appearance approximately 1.2 billion years ago after the separation of alveolates, whose genomes do not contain sequences directly related to GPCRs, from GPCR-expressing fungi and plants (Fredriksson and Schiöth, 2005). In known genomes, GPCR sequences are more abundant in nematodes and arthropods compared with plants or fungi, and even more so in vertebrates and mammals. These molecular entities are considered a tremendous success in the context of evolution; GPCRs can represent as much as 5% of the coding sequences in the genomes of some species (Fredriksson and Schiöth, 2005). In humans, the number of distinct GPCRs is estimated to be approximately 800, but many are orphan receptors since we do not yet know their natural ligands and functions (Fredriksson et al., 2003; Fredriksson and Schiöth, 2005). Great efforts are in progress to classify these receptors structurally and functionally (Fredriksson et al., 2003; Fredriksson and Schiöth, 2005; see also http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=694).

A dramatic evolution of thought and discovery has taken place over the last 100 years as researchers have begun defining these proteins as molecular entities instead of mere concepts. This has changed the understanding of physiologic and pathologic processes, the perception of cellular functions, medical education, and even clinical practice. A reflection of this ongoing revolution is the fact that two researchers, Robert J. Lefkowitz and Brian Kobilka, were awarded the Nobel Prize in Chemistry in 2012 (Kobilka, 2013; Lefkowitz, 2013; see also the corresponding sections on the Nobel Prize webpage at http://www.nobelprize.org/). The number of laboratories that have contributed to this field and continue to do so is enormous and is likely to continue growing.

As anticipated, GPCRs mediate a plethora of functions and are involved in the pathogenesis of many diseases. This latter aspect is frequently called the "dark side" of GPCRs but it is actually an opportunity that allows for therapeutic possibilities through pharmacological intervention. Advances using classic and molecular approaches are changing pharmacology. For example, the agonist (on)–antagonist (off) paradigm of how ligands modulate GPCR activity is now substituted by new ideas proposing that ligands induce a variety of active and inactive receptor conformations (see for example Audet and Bouvier, 2012; Manglik and Kobilka, 2014; Thanawala et al., 2014; Huang et al., 2015; DeVree et al., 2016). Operationally, these mechanisms might lead to different drug behaviors increasing the repertoire of pharmacodynamic possibilities, including full, partial, biased, and inverse agonism, as well as antagonism, allosteric modulation, and induction of internalization/degradation, among others (see for example Kenakin, 2009, 2015; Christopoulos, 2014; Roth and Bruggeman, 2014). This knowledge already has a profound effect on human

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ABBREVIATIONS: GPCR, G protein–coupled receptor; TRV130, *N*-[(3-methoxythiophen-2-yl)methyl]-2-[(9*R*)-9-pyridin-2-yl-6-oxaspiro[4.5]decan-9-yl]ethanamine.

therapeutics. For example, see the case of fingolimod (2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol; PubChem CID 107970), an agonist/functional antagonist that strongly promotes sphingosine 1-phosphate receptor internalization/-degradation, thereby modulating immune responses, and now serves a therapeutic role in the treatment of multiple sclerosis (Brinkmann et al., 2010; Choi et al., 2011). Another example is oliceridine (TRV130 or *N*-[(3-methoxythiophen-2-yl)methyl]-2-[(9*R*)-9-pyridin-2-yl-6-oxaspiro[4.5]decan-9-yl]ethanamine; PubChem CID 66553195), a G_i protein–biased agonist at μ-opioid receptors that produces weak β-arrestin recruitment (DeWire et al., 2013). Oliceridine is currently in clinical trials for treatment of acute pain and is expected to cause less respiratory depression, constipation, nausea, and tolerance than nonbiased opioid agonists. The world of biomedical science is just now beginning to see the tip of this conceptual iceberg, and many more exciting advances are on the horizon.

Molecular Pharmacology, published by the American Society for Pharmacology and Experimental Therapeutics, recently had its 50th anniversary (Brown et al., 2015). By publishing original high-quality work, this journal has made a commitment to disseminating crucial advances in receptor signaling and drug action. In addition, *Molecular Pharmacology* regularly publishes short reviews to provide the scientific community with concise leading opinions on recent developments and new perspectives on areas of increasing interest, as well as to point out neglected aspects and gaps in knowledge. Another aim of these reviews is to provide graduate students and professionals in related areas with "state-of-the-art" information. We were invited to act as guest editors for a special section containing a series of reviews on GPCRs that present views and ideas from researchers working in Latin America, with the aim of to highlight the outstanding science taking place in this part of the world and to foster international collaboration.

Cell communication and signaling has been studied by many Latin American scientists working in their own countries and abroad. A few examples include Bernardo Housay, who was awarded the Nobel Prize in Physiology and Medicine in 1947 for his work on pituitary hormones (Hawgood, 2004); Luis F. Leloir, who was awarded the Nobel Prize in 1970 for his research on glycogen metabolism (Krisman, 1996); and Eduardo Braun-Melendez, who was one of the discoverers of angiotensin (Basso and Terragno, 2001). Other notable Latin American researchers include Adolfo J. De Bold, who discovered atrial natriuretic factor (Braunwald, 2015); Maurício Rocha e Silva, who discovered bradykinin (Hawgood, 1997); Sérgio Henrique Ferreira, who described bradykinin-potentiating factors, which led to the development of angiotensin-converting enzyme inhibitors (Smith and Vane, 2003); Arturo Rosenblueth, who with Walter B. Cannon, greatly contributed to the understanding of adrenaline/noradrenaline actions (Shampo and Kyle, 1979); and Salvador Moncada, who made cardinal contributions to the prostaglandin and nitric oxide–cGMP fields (Baines, 2006). Also of particular significance is the work of prominent biophysicists who contributed to the understanding of membrane potential and cell responses triggered by ligand-activated channels (Elgoyhen and Barajas-López, 2016). The work of many other excellent researchers with important contributions cannot be mentioned because of space constraints, and so we express our apologies.

The fields of cell signaling and GPCR research are relatively new worldwide, initiated by the work of Sutherland and coworkers in the 1960s (Butcher and Robison, 1975) and then followed later by a flurry of groundbreaking advances in the 1980s and 1990s (Sunahara and Insel, 2016). In Mexico, for example, work in these areas initiated in the 1980s and has since slowly been attracting more groups (García-Sáinz and Rosenstein, 2007; Macías-Silva and Vázquez-Prado, 2011). A similar situation likely exists in other countries in the region. Regrettably, the number of laboratories working on these areas in our countries is not very large because projects and scientific careers in Latin America are frequently terminated or greatly delayed as a result of adverse social conditions, political turmoil, corruption/bad administration, and economic collapses. Unfortunately, this has been recurrent in most of our countries and a constant in the region. Nevertheless, there are laboratories in many Latin American countries that have produced outstanding work contributing to our current knowledge. This special section features minireviews by a selected group of leading Latin American scientists working on different aspects of GPCR function and regulation; it follows three other series published in *Molecular Pharmacology*, one featuring perspectives on ion channels by Latin American scientists (see the September 2016 issue) and two earlier groups of reviews on GPCRs (see the November 2014 and September 2015 issues).

In these minireviews by Latin American scientists, the authors cover a wide range of topics, including GPCRs for odorants (Malnic et al., 2016), histamine (Monczor and Fernández, 2016; Nieto-Alamilla et al., 2016), glutamate (Olmo et al., 2016), gonadotropins (Ulloa-Aguirre and Zarinan, 2016), cannabinoids (Olmo et al., 2016; Yudowski and Nogueras-Ortiz, 2016), CRF, angiotensin (Costa-Neto et al., 2016), and also some insights on $G\beta\gamma$ signaling (Vázquez-Prado et al., 2016). These include aspects on monogenic and monoallelic expression, ligand-receptor interactions and their pharmacodynamic consequences, receptor structure and interaction with other signaling elements, crosstalk, and regulation (Costa-Neto and Bouvier, 2016; Malnic et al., 2016; Monczor and Fernández, 2016; Nieto-Alamilla et al., 2016; Olmo et al., 2016; Slater et al., 2016; Ulloa-Aguirre and Zarinan, 2016; Vázquez-Prado et al., 2016; Yudowski and Nogueras-Ortiz, 2016). We hope that readers will find the articles to be of interest and that the ideas presented will help promote collaboration with colleagues in other parts of the world.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Pupo, García-Sáinz.

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