

Vol. 30 No. 2
April-June 2019

G-proteins coupled receptors

Receptores de membrana acoplados a proteínas G

Nayelli Nájera,* Rocío Pamela Martínez-Vega,* Andrés Portilla-Martínez,*
Pilar Ortiz-Vilchis,* Guillermo Ceballos*

Keywords:

Membrane receptors,
GPCR,
G-proteins.

Palabras clave:

Receptores
membranales,
GPCR,
proteínas G.

INTRODUCTION

The membrane receptors (GPCRs) coupled to regulatory binding proteins (G proteins), also known as R7G (receptors with 7 transmembrane domains, coupled to guanine nucleotide G proteins (*Figure 1*), heptahelical or serpentine receptors, form a large and ubiquitous protein superfamily, in charge of fundamental cellular functions.¹⁻³ In humans, more than 800 of such receptors have been cloned, although a great proportion of them remains orphaned (without known ligand), while many others have been poorly, structurally and functionally, characterized. A wide variety of natural and synthetic molecules (such as hormones, neurotransmitters, autacoids, nutrients, ions, photons, substances involved in odor and taste, and a wide variety of pharmacological agents) exert their stimulatory or inhibitory actions through interaction with these receptors. Examples of these ligands are adrenergic hormones, acetylcholine, serotonin, histamine, adenosine, bradykinin, vasoactive intestinal polypeptide, cannabinoids, opioids, and some pheromones, among many other molecules.^{4,5} Under the light of this knowledge, numerous drugs have been designed or have been found to be useful in antagonizing or stimulating these receptors in a variety of clinical conditions, as hypertension, heart failure, obesity, type 2 diabetes mellitus, renal damage, antiplatelet therapy, neurodegenerative diseases (as Alzheimer's, Parkinson's and Huntington's diseases and some forms of vascular and senile dementia), bronchial asthma, macronodular adrenal hyperplasia and adrenal Cushing syndrome, pain and itch, as well as immunity and inflammation, among many other more.⁶⁻¹⁵

A great proportion of current approved drugs and others that will be introduced in the near future, target GPCRs, fact that underlines the clinical importance of this receptor family.^{3,16}

Clinicians, practical recipients of this basic knowledge, must know more deeply the function and consequences of these agonist/antagonist-receptor relationships, in order to better understand both; the basic molecular mechanisms of some diseases, as well as the mode of action of agonist and antagonist agents in many clinical settings.

Examples of types and actions of GPCRs. The hierarchical structure of GPCR superfamily is rather complex.³ It is composed by, at least, seven independent families, each of which is categorized in several subfamilies and sub-subfamilies, which are subdivided in turn in a number of subtypes. According with the A-F system of notation,³ the seven basic families of GPCRs are: class A (rhodopsin like); class B (secretin like); class C (metabotropic glutamate/pheromone, and associated vomeronasal, V1R and V3R, and taste receptors, T2R); class D (the fungal mating pheromone); class E (cyclic AMP, cAMP receptors); class F (the frizzled, FZD, and smoothened, SMO receptors); and finally the adhesion family, which is not identified by any letter in this notation system.¹⁷

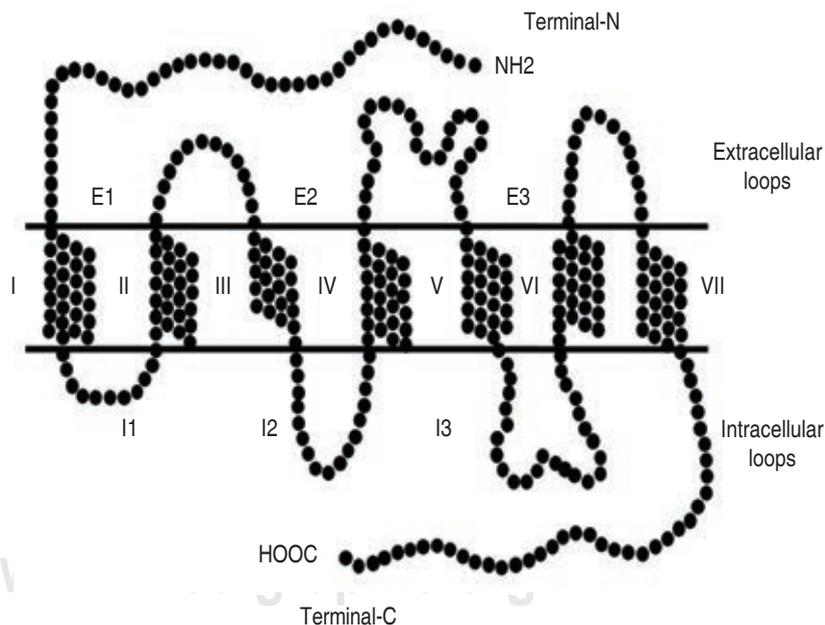
Some of the more abundant and better studied GPCRs, with paramount importance in clinical medicine, pertain to class A. For example, the rhodopsin-like receptors, expressed in retina, are specialized in phototransduction, (the conversion of light in a biochemical cascade signaling to produce vision).¹⁸ The adrenergic receptors, α and β adrenoceptors (the best studied of this superfamily), whose ligands are catecholamines, also belong to this

* Laboratorio de
Investigación Integral
Cardiometabólica,
Sección de Posgrado,
Escuela Superior de
Medicina, Instituto
Politécnico Nacional,
Mexico City, Mexico.

Received:
28/05/2019
Accepted:
03/06/2019

family. Also belong to class¹⁹ As it is known, adrenergic stimulation is one of the executive branches of the autonomic nervous system, involved in multiple functions related to heart function, arterial tone, nervous reflexes, smooth muscle tone of several structures (ureters, gastrointestinal tube, bronchioles, pregnant uterus, etc.), metabolic actions on insulin and glucagon, increased lipolysis, thermogenesis, renin secretion, brain functions as the handling of sensorial stimuli, memory processing, and other pre-frontal cognitive abilities, among many others. GPCRs of the same class, the muscarinic acetylcholine receptors,²⁰ mediate the actions of the other autonomic branch, the parasympathetic system, whose actions, in general, are dialectically opposed to those of the adrenergic system. Also to this class A pertain adenosine receptors,²¹ responsible of the multiple pleiotropic effects of this autacoid, a precursor of phosphate organic complexes: cyclic adenosine monophosphate (cAMP), adenosine diphosphate, and adenosine triphosphate (ADP and ATP respectively). ATP,

as it is known stores and releases the energy produced principally by the three power causeways: the phosphagen system, anaerobic glycolysis (Embden-Meyerhof pathway) and the tandem-like systems of aerobic glycolysis-electron transport chain (Krebs cycle and mitochondrial respiratory chain complex). The lack of oxygen availability during an episode of ischemia, reduces the aerobic production of ATP, diminishing or suppressing Krebs cycle, the most profitable and efficient system of production and storage of energy. A «reverse cascade» then takes place, because secondary to the decrease of ATP production, increases proportionally the accumulation of its precursors, ADP, then AMP and finally, adenosine. The latter, acting on a specific GPCR receptor increase nitric oxygen bioavailability, regulating coronary flow according to metabolic myocardial demands (adenosine hypothesis or Berne & Rubio mechanism),²² attenuating at the same time myocardial contractility and myocardial oxygen consumption caused by adrenergic stimulation. In addition, adenosine diminishes



GPCRs receptors are characterized by seven α -helical trans-membrane domains (I-VII), three extracellular (E) loops and three intracellular (I) loops. Agonists are nested in sites of the extracellular loops, while intracellular terminal-C is related with the translator G proteins.

Figure 1: Molecular structure of GPCRs.

sinusal activity, slows atrial-ventricular (A-V) conduction, and shortens atrial action potential duration and refractoriness, reducing also ventricular automatism, without influencing His-Purkinje conduction velocity.²³

Receptors that mediate the action of different members of angiotensin family appertain also to class A GPCRs.²⁴ The most important are angiotensin II type 1 receptor (AT₁ receptor) and the angiotensin II counter-regulatory type 2 receptor (AT₂).²⁵ Oncogene mas acts as a putative receptor for angiotensin 1-7, in charge of the most important counter-regulation mechanism of angiotensin II, opposing all systemic and local actions of the latter hormone.²⁶ Angiotensin II, when it interacts with the AT₁ receptors, causes systemic effects as arteriolar vasoconstriction, lessening of renal flow with increase of intra-glomerular pressure, rise of peripheral resistance and blood pressure, release of hormones like aldosterone and antidiuretic hormone, expansion of intravascular volume, and stimulation of thirst. And also, at local level, the activation of AT₁ receptors, via several signaling pathways give place to a series of beneficial phenomena regulating tissue and vascular defense and repair, but when deregulated impose serious functional and structural damage caused due to proinflammatory, prooxidative, pro-proliferative, prothrombotic and proapoptotic effects.²⁷

A little less studied, but arousing a growing interest, are the class B GPCRs,²⁸ named the secretin family, involved in fundamental functions as glucose homeostasis, via peptide ligands as glucagon, as well as intestinal incretin hormones, glucagon-like peptide (GLP 1 and 2) and glucose-dependent insulinotropic peptide (GIP).^{29,30} These peptides, mainly GLP-1, lower blood glucose, stimulating the formation of insulin, via gene transcription, islet cell growth, and neogenesis of β -cells, as well as favoring the hormone secretion. All these actions are carried out by activation of a specific class B GPCR. The enzyme dipeptidyl peptidase 4 (DPP-4) that rapidly inactivates intestinal incretin is inhibited by agents called gliptins (or DPP-4 inhibitors, as sitagliptin, linagliptin and alogliptin), which prolong the biological life of GLP-1, a mechanism that

gives them an important place in antidiabetic therapy.³¹ In the same way, the analogues of GLP-1 (i.e. exenatide), fulfill the same purpose. Other members of this family are the types 1 and 2 corticotropin releasing factor (CRF) receptors.³² CRF is their main ligand, activating the production of the adrenocorticotrophic hormone (ACTH) in anterior pituitary gland, which in turn stimulates the production of cortisol in the cortex of adrenal glands. As it is well known, cortisol produces a variety of responses to many stressors. CRF acting in its receptor increases adrenergic activity, while parasympathetic decreases. CRF and urocortin,³³ a related peptide ligand, suppress appetite, having the latter much more power in this regard. calcitonin,³⁴ a thyroid hormone, also a member of this family, regulates calcium homeostasis; inhibiting bone osteoclast activity and increasing at the same time renal calcium excretion. Related peptides are calcitonin gene-related peptide (CGRP) and amylin, with a complex set of functions: renal flow control, glucose homeostasis, inhibition of bone reabsorption, satiety, etc. Other members of this family are the parathyroid hormone receptors involved in calcium and phosphorous metabolism,³⁵ and the vasoactive intestinal polypeptide (VIP),³⁶ which despite its name is produced in different parts of the body and has a relaxing effect on smooth muscle of gastrointestinal tract and blood vessels, but also is involved in many other gastrointestinal, biliary and pancreatic functions. Also, VIP serves as a non-adrenergic, non-cholinergic neurotransmitter, regulating many circadian rhythms. Furthermore, it has been discovered that the polypeptide has an important role as regulator of coronary tone and flow, contributing also to heart contractility and rate.

Class C GPCRs (metabotropic glutamate/pheromone receptors)³⁷ forms a large family composed by metabotropic glutamate (mGlu), gamma-aminobutyric acid_B (GABA_B), Ca²⁺-sensing (CaS), and taste and odor receptors. mGlu receptors intervenes in synaptic transmission and excitability of neuronal cells.³⁸ Their action could be used therapeutically in a wide set of psychiatric and neurodegenerative disorders.³⁹ GABA (gamma-aminobutyric acid) is the main

inhibiting neurotransmitter of the central nervous system, weakening the transmission of neural signal. It uses two types of receptor: type A (GABA_A) functions as ligand-gated transmembrane ion channels (ionotropic receptors), while type B (GABA_B) acts as GPCRs, transmitting their signal via G proteins and a second messenger (metabotropic action). The intracellular actions include inhibition of adenylyl cyclase, which in turn inhibits the voltage-dependent calcium channels, and doing so induces a long-sustained synaptic transmission inhibition, later and slower in comparison with which is caused by type A GABA.^{40,41} GABA_B agonism effects can be used in the management of pain, as an inhibitor of nociceptive transmission in afferent fibers, but sufficient clinical evidence is still lacking. These drugs have also promissory evidence in neuropathic pain and spastic disorders. Also, GABA_B agonists have been tested for the treatment of alcohol and cocaine addiction and a series of psychiatric and neurological conditions. CaS (calcium sensing receptor) is a unique GPCR, synthesized in both parathyroid glands and kidneys, whose ligands are Ca⁺⁺ ions. The receptor intervenes in calcium homeostasis regulating the secretion of parathyroid hormone. Allosteric agonists, acting as calcium mimetics have been tested with certain success in various metabolic calcium disorders, as hyperparathyroidism, some kinds of hypocalcemia and osteopenia/osteoporosis.⁴²

The vomeronasal organ (VNO) has crucial importance in many inferior animals. Located in the highest part of the nasal septum, serves a detecting organ of pheromones and scent molecules, which in turn yields to multiples effects on animal social, mating, and preying behavior.^{43,44} Although it was thought that VNP did not exist at all in humans, there is convincing evidence that shows its existence, although less developed than in lower mammals and reptiles. Unlike what happens in lower animals that have a pair of these organs, in humans, it is usually unilateral, without neural connections.^{43,44} Surely, VNO (Jacobson organ) in humans represent a non-operational, fading basic chemical communication system with members of our same species.⁴⁴ Notwithstanding, there are

some evidences signaling the existence of human pheromones, steroids produced in the skin that can elicit certain sex hormones modifications in men and women.⁴⁵ Regarding the savor sense, there are six basic tastes: sweetness, bitterness, *umami* (from the Japanese term *umai* meaning delicious or savory), and the taste of fat caused by the detection of free fatty acids in food («oleogustus»), sourness, and saltiness.⁴⁶⁻⁴⁸ The first four are detected by GPCRs expressed in specialized test cells located in gustatory tongue papillae and other portions of the oropharyngeal cavity.⁴⁹ Among taste disorders, are known the absolute absence of taste (ageusia), the reduction of this sense (hypogeusia), the confusion in determining different tastes (dysgeusia), and the permanence of a taste, generally unpleasant, that does not correspond to any meal or substance swallowed (phantom taste).⁵⁰ Taste sensing and signaling in mammals, including humans is an extremely complex function. A part of the cluster of chemical signs and receptors involved in this matter, GPCRs are expressed in some type II cells from the bud taste and contribute to the build-up of tasting sense. Taste dysfunction can be observed in a bunch of acute and chronic diseases and conditions, such as viral flu infections, VIH, ageing, diabetes, autoimmune diseases, cancer, nutritional deficiencies, as effects of ionizing radiations, and drugs side-effects, among many others.^{50,51} In this regard, antagonists of the AT₁ angiotensin II receptors reduce taste sensitivity by already unclear mechanisms, while the metallic phantom-taste frequently observed with the chronic use of the ACE inhibitor captopril is related to its thiol-group which can form chelated zinc compounds.⁵² So far, has not been elucidated the possible involvement of GPCRs Class B and C in taste disorders.

The remaining GPCRs families, class D, E, F and adhesion have been, so far, less studied. D class serves mating responses in fungi,³ while class E receptors were found in *Dictyostelium discoideum*, a lime mold that can live as a unicellular amoeba, but in certain circumstances can aggregate with other of its own species to form multicellular beings.⁵³ Class F is composed by Frizzled and Smoothed (SMO) proteins in human beings, playing several roles in cancerogenesis, stem

cells and embryo development.^{54,55} Finally, in humans the adhesion family consists of 33 receptors the effects of some members of this family have been related to organogenesis, neurodevelopment, myelination, angiogenesis, and cancer progression.⁵⁶

Structure of GPCRs

GPCR receptors are known as seven transmembrane receptors (7TM), as their common feature is the presence of seven α -helical transmembrane domains (TM 1-7) combined with

three extracellular loops and three intracellular loops (Figure 1).⁵⁶⁻⁵⁹ Specific segments of the extracellular loops are the place where ligands interact with the receptors, while the intracytosolic loops are in contact with G proteins. The external terminus of the peptide chain contains an amide group (NH₂), while the internal has a carboxyl group (COOH). The single polypeptide of many GPCRs has among 290 to 951 aminoacid residues (Figure 1).

Guanine nucleotide-binding proteins (G proteins, GPs) are specialized in signal transducing (Figure 2).⁶⁰ A group of them, are heterotrimeric

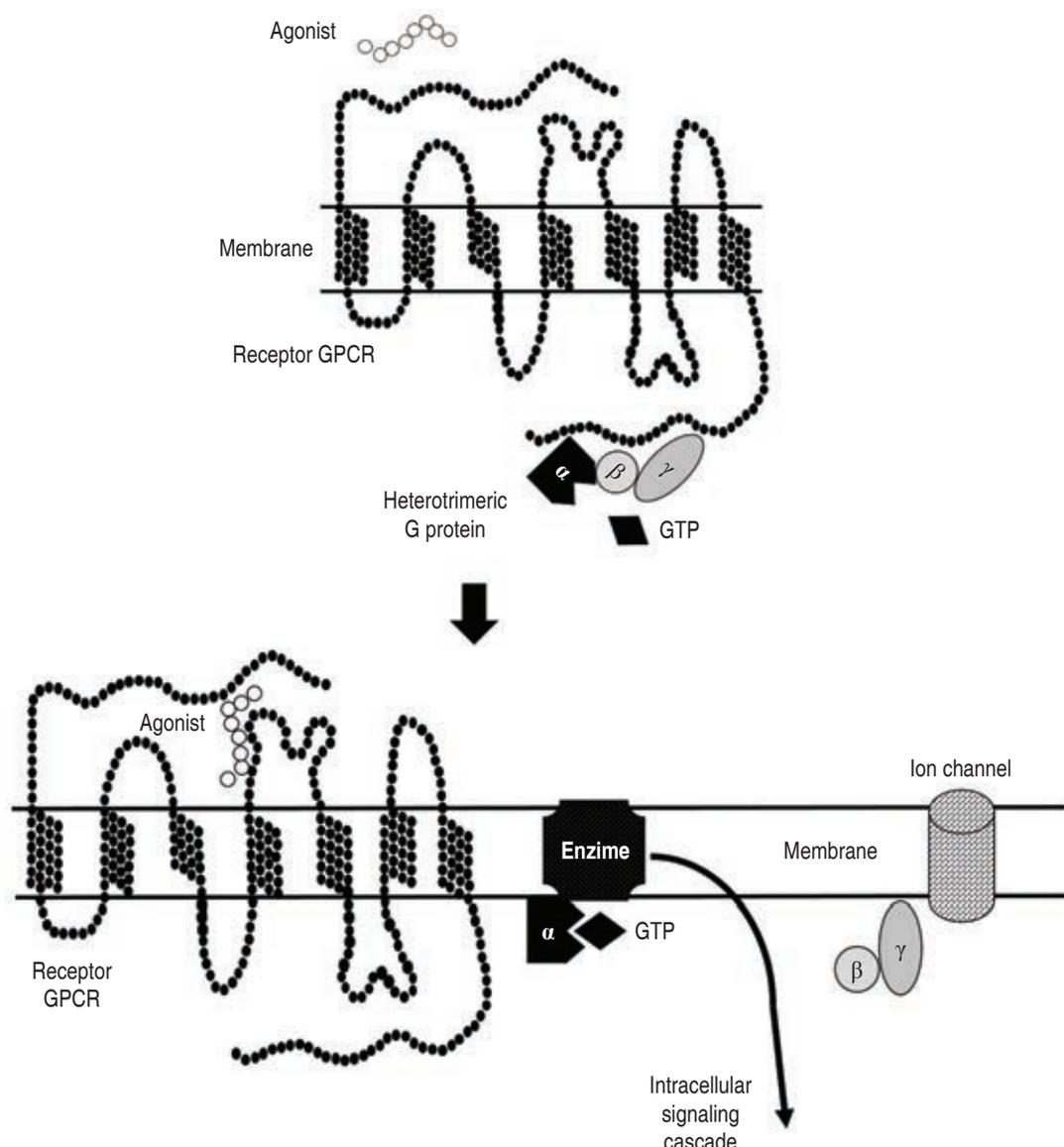


Figure 2:
Function of GPCR receptors.

proteins, i.e., formed by three different structurally independent subunits, named α , β , and γ . G_α contains guanosine triphosphate (GTP),⁶¹ one of the energy transfers formed in the Krebs cycle. G_α is bound to the internal structure of the receptor, as well to a composed unit formed with β and γ subunits. This is the arrangement when the receiver is in an inactivate state. When an agonist nests in the external portion of the receptor, an allosteric change of shape and function of G_α takes place. G_α has GTPase activity, converting GTP in guanine diphosphate (GDP), and releasing energy. By acting in such way, G_α behaves as an activation/deactivation switch of many transducing processes. When GTP is activated, the trimeric structure is broken, but β and γ subunits stay together, and elicit their own intracellular or membrane effects, while liberated G_α can freely interact with other substrates or effectors, in the vicinity of cell membrane, forming molecules who play the role of second messengers in the signaling cascade. Once GTP is converted in GDP, G_α enters in a phase of rest, and the three subunits are reunited, recovering their basal trimeric nature.^{57,58}

A simplified example of the above is provided by the interaction of angiotensin II with AT_1 receptor (Figure 2).⁶² The octapeptide interacts with the extracellular orthosteric binding site, in the loop E2, activating the receptor and initiating a conformational and functional change in G_α . When G_α is freed goes to the membrane and in turn, activates the enzyme phospholipase C (PLC), which among other functions, hydrolyze a constitutive membrane phospholipid, phosphatidylserine, producing two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). The former, without leaving the membrane activates protein kinase C (PKC), a multifaceted messenger, which phosphorylating several proteins, exerts a number of functions, among them, muscle contraction and growth (is one of the reasons why angiotensin II is a vasoconstrictor, as well as a growth promoter). On the contrary, IP3 abandon the membrane in which is produced, and reaches the endoplasmic/sarcoplasmic reticulum, and through a specific receptor allows the exit of Ca^{++} to the cytosol, in favor of its osmotic gradient. Ca^{++} has several

functions, as facilitating muscle contraction and cell proliferation.

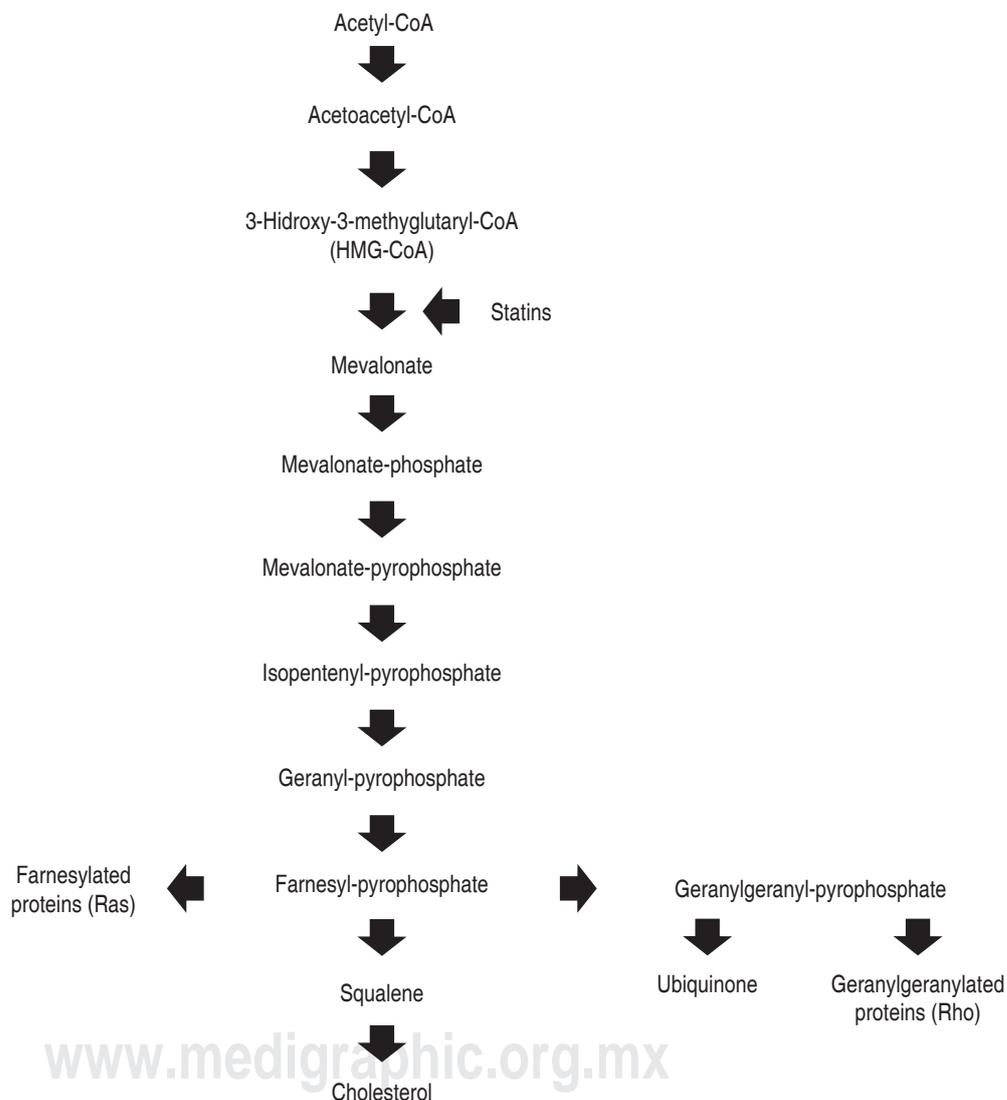
For more complexity, G_α is not a single protein, but indeed form an enter family of different classes. There are varieties of the protein with particular functions, pertaining to several GPCRs. At least are recognized four groups of these G_α subunits: $G\alpha_s$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$. For example, $G\alpha_s$ stimulates the enzyme adenylyclase, forming at the end cAMP, a second messenger involved in multiple signaling processes. On the contrary, $G\alpha_i$ is composed by a large number of inhibitory proteins which inhibits adenylyclase and reduces the amount of cAMP. $G\alpha_q$ activates PLC, generating the abovementioned second messengers DAG and IP3. Finally, $G\alpha_{12}$ (also called $G\alpha_t$ or transducin), is specialized in photo-transduction in the retina.⁶³

There is another family of small monomeric G proteins akin to G_α , which function as GTPases.^{64,65} As their similar greater GPs, they behave as binary switches of multiple cellular functions (as cytoskeletal organization, polarity, gene expression, cell differentiation, mobility, lipid endocytic trafficking, etc.)⁶³ in a cyclic GTP/DGP sequence controlled by regulatory proteins, some of them stimulating GTP formation, while others promoting the conversion to GDP (GDP/GTP-exchange factors and GDP-dissociation inhibitors, respectively). As the bigger GPCRs, small GPs are activated when bound to GTP and become inactivated when GTP switches to GDP. GPs are assembled in large families. Members of the Ras family (the name comes from *rats sarcoma*,^{66,67} animal model in which they were discovered) are involved in cell proliferation and cancer genesis (they are oncogenes), although many of them are in fact tumor suppressors. A homologous group, known for that reason as Rho family is also intermingled in a copious amount of cellular processes, mainly, cell morphology and mobility. Other important groups of these small GTPases are Rab, Ran, Miro and Arf families.⁶⁵

An example of the function of these small monomeric molecules is their relationship with the mevalonate cascade, which final product is cholesterol (Figure 3).⁶⁸ The rate-limiting step for cholesterol biosynthesis is the activity of the enzyme 3-hidroxi-3-metil-glutaril-CoA reductase

(HMG-CoA), which is inhibited by statins. In this cascade, are produced also intermediate non-sterol metabolites, isoprenoids as isopentenyl pyrophosphate, farnesyl and geranylgeranyl diphosphates (FPP and GGPP), dolichol and ubiquinone. Using specific transferases, FPP and GGPP attaches farnesyl or geranylgeranyl moieties to the protein to be modified. This posttranslational modification is known as

prenylation or farnesylation, which allow small GPs to be attached in the cell lipid membrane, where they can interact with specific receptors, initiating or modulating several signal transduction systems, getting going, for example several phenomena as cell proliferation, differentiation, apoptosis, or cytoskeleton organization.⁶⁹ This is the reason why statins, apart from the reduction of *de novo* cholesterol production, exert the so-



The mevalonate pathway leads on one hand to the biosynthesis of *de novo* cholesterol, but also to the formation of intermediate, non-steroidal metabolites, isoprenoid compounds, whose function is the prenylation or farnesylation of proteins, among them, small monomeric G proteins, involved in the implementation of many inflammatory, apoptotic, degenerative and proliferative processes.

Figure 3: Generation of small G proteins the mevalonate pathway.

called «pleiotropic» beneficial actions, decreasing the biological effects of small GPs.

CONCLUSION

The GPCR family is involved in many physiologic processes and has a role in numerous biopathological mechanisms of multiple diseases. Currently, a great number of drugs target diverse CGPR, as was discussed in the text. In the near future an even greater number of drugs will be used to inhibit or stimulate these receptors, and induce therapeutic modifications in a variety of pathologies.

The clinician dedicated primarily to the care, diagnosis and treatment of patients will better perform its important missions if it is able to introduce in her or his mental mechanisms the concepts derived from the knowledge of the interaction among agonists and antagonists with the vast variety of receptors that must be considered therapeutic targets.

REFERENCES

- Rosenbaum DM, Rasmussen SGF, Kobilka BK. The structure and function of G-protein-coupled receptors. *Nature*. 2009; 459: 356-363.
- Strosberg AD. Structure/function relationship of proteins belonging to the family of receptors coupled to GTP-binding proteins. *Eur J Biochem*. 1991; 196: 1-10.
- Hu GM, Mai TL, Chen CM. Visualizing the GPCR network: Classification and evolution. *Scientific Reports*. 2017; 7: 15495.
- Wacker D, Stevens RC, Roth BL. How ligands illuminate GPCR molecular pharmacology. *Cell*. 2017; 170: 414-427.
- Katritch V, Cherezov V, Stevens RC. Structure-function of the G-protein-coupled receptor superfamily. *Annu Rev Pharmacol Toxicol*. 2013; 53: 531-556.
- Riddy DM, Delerive P, Summers RJ, Sexton PM, Langmead CJ. G protein-coupled receptors targeting insulin resistance, obesity, and type 2 diabetes mellitus. *Pharmacol Rev*. 2018; 70: 39-67.
- Wang J, Gareri C, Rockman HA. G-Protein-coupled receptors in heart disease. *Circ Res*. 2018; 123: 716-735.
- Reimann F, Gribble FM. G protein-coupled receptors as new therapeutic targets for type 2 diabetes. *Diabetologia*. 2016; 59: 229-233.
- Park F. Activators of G Protein signaling in the kidney. *J Pharmacol Exp Ther*. 2015; 353: 235-242.
- Gurbel PA, Kuliopulos A, Tantry US. G-Protein-Coupled receptors signaling pathways in new antiplatelet drug development. *Arterioscler Thromb Vasc Biol*. 2015; 35: 500-512.
- Huang Y, Todd N, Thathiah A. The role of GPCRs in neurodegenerative diseases: avenues for therapeutic intervention. *Curr Opin Pharmacol*. 2017; 32: 96-110.
- Billington CK, Pen RB. Signaling and regulation of G protein-coupled receptors in airway smooth muscle. *Respir Res*. 2003; 4: 2.
- Assie G, Louisset E, Sturm N, René-Corail F, Groussin L, Bertherat J et al. Systematic analysis of G protein-coupled receptor gene expression in adrenocorticotropin-independent macronodular adrenocortical hyperplasia identifies novel targets for pharmacological control of adrenal Cushing's syndrome. *J Clin Endocrinol Metab*. 2010; 95: E253-E262.
- Geppetti P, Veldhuis NA, Lieu TM, Bunnett NW. G Protein-coupled receptors: dynamic machines for signaling pain and itch. *Neuron*. 2015; 88: 635-649.
- Lin HH, Hsiao CC, Pabst C, Hébert J, Schöneberg T, Hamann J. Adhesion GPCRs in regulating immune responses and inflammation. *Adv Immunol*. 2017; 136: 163-201.
- Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. *Nat Rev Drug Discov*. 2017; 16: 829-842.
- Paavola KJ, Hall RA. Adhesion G protein-coupled receptors: signaling, pharmacology, and mechanisms of activation. *Mol Pharmacol*. 2012; 82: 777-783.
- Mustafi D, Palczewski K. Topology of class A G protein-coupled receptors: insights gained from crystal structures of rhodopsins, adrenergic and adenosine receptors. *Mol Pharmacol*. 2009; 75: 1-12.
- Ciccarelli M, Sorriento D, Coscioni E, Iaccarino G, Santulli G. Adrenergic receptors. *academic press*. London UK: *Endocrinology of the Heart in Health and Disease: Integrated, Cellular, and Molecular Endocrinology of the Heart*; 2009. pp. 285-315.
- Eglen RM. Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. *Auton Autacoid Pharmacol*. 2006; 26: 219-233.
- Sheth S, Brito R, Mukherjee D, Rybak LP, Ramkumar V. Adenosine receptors: expression, function and regulation. *Int J Mol Sci*. 2014; 15: 2024-2052.
- Berne RM. The role of adenosine in the regulation of coronary blood flow. *Circ Res*. 1980; 47: 807-813.
- Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine. Basic and clinical concepts. *Circulation*. 1991; 83: 1499-1509.
- Singh KD, Karnik SS. Angiotensin receptors: structure, function, signaling and clinical applications. *J Cell Signal*. 2016; 1: 111.
- Li Y, Li XH, Yuan H. Angiotensin II type-2 receptor-specific effects on the cardiovascular system. *Cardiovasc Diagn Ther*. 2012; 2: 56-62.
- Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M. The ACE2/angiotensin-(1-7)/MAS axis of the renin-angiotensin system: Focus on angiotensin-(1-7). *Physiol Rev*. 2018; 98: 505-553.
- Lavoie JL, Sigmund CD. Minireview: overview of the renin-angiotensin system--an endocrine and paracrine system. *Endocrinology*. 2003; 144: 2179-2183.
- Bortolato A, Doré AS, Hollenstein K, Tehan BC, Mason JS, Marshall FH. Structure of Class B GPCRs: new

- horizons for drug discovery. *Br J Pharmacol.* 2014; 171: 3132-3145.
29. Thorens B. Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. *Proc Natl Acad Sci USA.* 1992; 89: 8641-8645.
 30. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. *J Diabetes Investig.* 2010; 1: 8-23.
 31. MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AMF, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes.* 2002; 51 (suppl 3): S434-S442.
 32. Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. *CNS Neurol Disord Drug Targets.* 2006; 5: 453-479.
 33. Slater PG, Yarur HE, Gysling K. Corticotropin-releasing factor receptors and their interacting proteins: functional consequences. *Mol Pharmacol.* 2016; 90: 627-632.
 34. Masi L, Brandi ML. Calcitonin and calcitonin receptors. *Clin Cases Miner Bone Metab.* 2007; 4: 117-122.
 35. Vilardaga JP, Romero G, Friedman PA, Gardella TJ. Molecular basis of parathyroid hormone receptor signaling and trafficking: a family B GPCR paradigm. *Cell Mol Life Sci.* 2011; 68: 1-13.
 36. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. *Cardiovasc Res.* 2001; 49: 27-37.
 37. Chun L, Zhang WH, Liu JF. Structure and ligand recognition of class C GPCRs. *Acta Pharmacol Sin.* 2012; 33: 312-323.
 38. Pin JP, Acher F. The metabotropic glutamate receptors: structure, activation mechanism and pharmacology. *Curr Drug Targets CNS Neurol Disord.* 2002; 1: 297-317.
 39. Simeone TA, Sanchez RM, Rho JM. Molecular biology and ontogeny of glutamate receptors in the mammalian central nervous system. *J Child Neurol.* 2004; 19: 343-360.
 40. Rondard P, Goudet C, Kniazeff J, Pin JP, Prezeau L. The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABAB class C G protein-coupled receptors. *Neuropharmacology.* 2011; 60: 82-92.
 41. Betke KM, Wells CA, Hamm HE. GPCR mediated regulation of synaptic transmission. *Prog Neurobiol.* 2012; 96: 304-321.
 42. Grupo de estudio CINAREN, Torregrosa JV, Morales E, Díaz JM, Crespo J, Bravo J et al. Cinacalcet en el manejo del hiperparatiroidismo secundario normocalcémico tras el trasplante renal: estudio multicéntrico de un año de seguimiento. *Nefrología.* 2014; 34: 62-68.
 43. Francia S, Pifferi S, Menini A, Tirindelli R. Vomeronasal receptors and signal transduction in the vomeronasal organ of mammals. In: Mucignat-Caretta C, editor. *Neurobiology of chemical communication.* Chapter 10. Boca Raton (FL): CRC Press/Taylor & Francis; 2014.
 44. Meredith M. Human vomeronasal organ function: a critical review of best and worst cases. *Chem Sens.* 2001; 26: 433-445.
 45. Trotier D. Vomeronasal organ and human pheromones. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2011; 128: 184-190.
 46. Sanematsu K, Yoshida R, Shigemura N, Ninomiya Y. Structure, function, and signaling of taste G-protein-coupled receptors. *Curr Pharm Biotechnol.* 2014; 15: 951-961.
 47. Melis M, Tomassini-Barbarossa IT. Taste perception of sweet, sour, salty, bitter, and umami and changes due to l-Arginine supplementation, as a function of genetic ability to taste 6-n-propylthiouracil. *Nutrients.* 2017; 9: 541.
 48. Running CA, Craig BA, Mattes RD. Oleogustus: the unique taste of fat. *Chem Senses.* 2015; 40: 507-516.
 49. Cygankiewicz AI, Maslowska A, Krajewska WM. Molecular basis of taste sense: involvement of GPCR receptors. *Crit Rev Food Sci Nutr.* 2014; 54 (6): 771-780.
 50. Amballdhage VK, Puttabuddi JH, Nunsavath PN, Tummuru YR. Taste disorders: A review. *JIAOMR.* 2014; 26: 69-76.
 51. Feng P, Huang L, Wang H. Taste bud homeostasis in health, disease, and aging. *Chem Senses.* 2014; 39: 3-16.
 52. Henkin RI. Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Saf.* 1994; 11: 318-377.
 53. Prabhua Y, Mondal S, Eichinger L, Noeje AA. A GPCR involved in post aggregation events in *Dictyostelium discoideum*. *Develop Biol.* 2007; 312: 29-43.
 54. Basith S, Cui M, Macalino SJY, Park J, Clavio NAB, Kang S et al. Exploring G protein-coupled receptors (GPCRs) ligand space via cheminformatics approaches: Impact on rational drug design. *Front Pharmacol.* 2018; 9: 128.
 55. Wright SC, Kozielowicz P, Kowalski-Jahn M, Petersen J, Bowin CF, Slodkovicz G et al. A conserved molecular switch in class F receptors regulates receptor activation and pathway selection. *Nature Communication.* 2019; 10: 667.
 56. Bjarnadóttir TK, Fredriksson R, Schiöth HB. The adhesion GPCR: a unique of G protein-coupled receptors with important roles in both central and peripheral tissues. *Cell Mol. Life Sci.* 2007; 64: 2014-2119.
 57. Kobilka BK. G protein coupled receptor structure and activation. *Biochim Biophys Acta.* 2007; 1768: 794-807.
 58. Gurevich VV, Gurevich EV. Molecular mechanisms of GPCR signaling: a structural perspective. *Int J Mol Sci.* 2017; 18: 2519.
 59. Rosenbaum DM, Rasmussen SCF, Kobilka BK. The structure and function of G-protein-coupled receptors. *Mol Pharmacol.* 2012; 82: 777-783.
 60. Birnbaumer L. The discovery of signal transduction by G proteins: a personal account and an overview of the initial findings and contributions that led to our present understanding. *Biochim Biophys Acta.* 2007; 1768 (4): 756-771.
 61. Milligan G, Kostenis E. Heterotrimeric G-proteins: a short history. *Br J Pharmacol.* 2006; 147 (Suppl 1): S46-S55.
 62. Griendling KK, Murphy TJ, Alexander RW. Molecular biology of the renin-angiotensin system. *Circulation.* 1993; 87: 1816-1828.
 63. Syrovatkina V, Alegre KO, Dey R, Huang XY. Regulation, signaling and physiological functions of G-proteins. *J Mol Biol.* 2016; 428: 3850-3868.
 64. Heider D, Hauke S, Pyka M, Kessler D. Insights into the classification of small GTPases. *Adv Appl Bioinforma Chem.* 2010; 3: 15-24.

65. Song S, Cong W, Zhou S, Shi Y, Dai W, Zhang H et al. Small GTPases: structure, biological function and its interaction with nanoparticles. *Asian J Pharm Sci.* 2019; 14: 30-39.
66. Wennerberg K, Rossman KL, Der CJ. The Ras superfamily at a glance. *J Cell Sci.* 2005; 118: 843-846.
67. Colicelli J. Human RAS superfamily proteins and related GTPases. *Sci STKE.* 2004; (250): RE13.
68. Hashemi M, Hoshyar R, Ande SR, Chen QM, Solomon C, Zuse A et al. Mevalonate cascade and its regulation in cholesterol metabolism in different tissues in health and disease. *Curr Mol Pharmacol.* 2017; 10: 13-26.
69. Alizadeh J, Zeki AA, Mirzae N, Tewary S, Moghadam AR, Glogowska A et al. Mevalonate cascade inhibition by simvastatin induces the intrinsic apoptosis pathway via depletion of isoprenoids in tumor cells. *Scientific Reports.* 2017; 7: 44841.

Correspondence to:

Nayelli Nájera
E-mail: nnajerag@ipn.mx

www.medigraphic.org.mx