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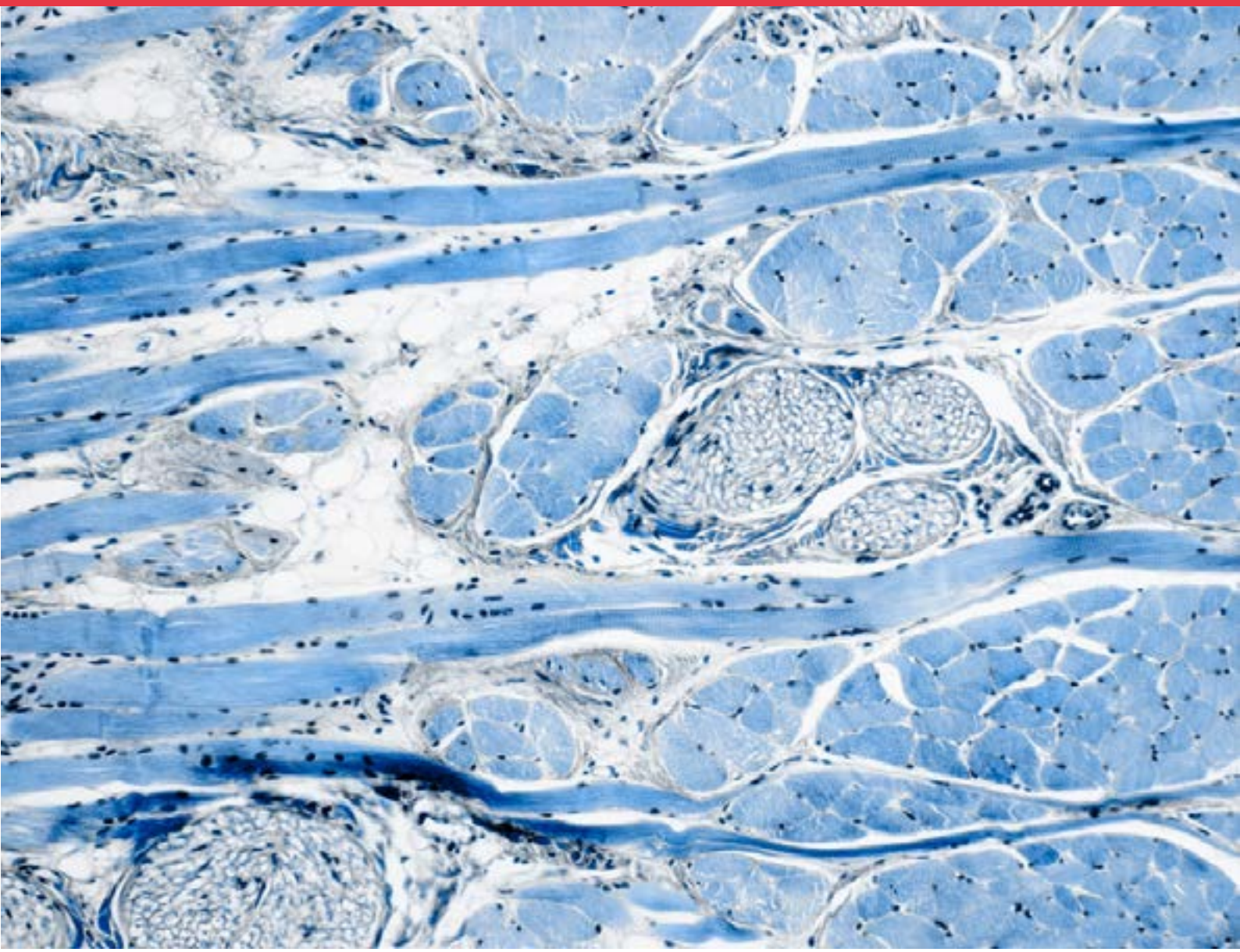

Vol. 17, May-June, 2024
ISSN 1669-5410 (Online)
pmr.safisiol.org.ar

Physiological
Mini
Reviews

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Physiological Mini-Reviews

[ISSN 1669-5410 (Online)]

Journal address: Cellular and Molecular Physiology Laboratory (CMPL).Department of Obstetrics. Division of Obstetrics and Gynaecology. Marcoleta 391, Santiago 8330024, Chile
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THE PROTECTIVE AXIS OF THE RENIN-ANGIOTENSIN SYSTEM AND INFLAMMATION: IMPLICATIONS OF RECEPTOR HETEROMERIZATION

Ezequiel F. Bruna-Haupt [1], and Mariela M. Gironacci [2] *

[1] Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis (UNSL), San Luis, Argentina.
[2] Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, IQUIFIB (UBA-CONICET), Buenos Aires, Argentina.

***correspondence to**: mariela@qb.ffyb.uba.ar; marielagironacci@gmail.com

Abstract
Hypertension is one of the major health challenges in today's society. Cardiovascular diseases represent the leading cause of morbidity and mortality in Western countries. Inflammation plays a significant role in the pathogenesis of hypertension. Various subpopulations of cells involved in innate and adaptive immune responses, through the production of various proinflammatory cytokines, contribute to hypertension development. One therapeutic target in the treatment of hypertension is the renin-angiotensin system (RAS). The RAS comprises two axes with opposing effects: the classic pressor pro-inflammatory axis and the counter-regulatory protective anti-inflammatory axis. Imbalances in these axes favor excessive inflammation, exacerbating the hypertensive condition. This review focuses on the response triggered by the protective axis of the RAS in inflammation and how it may be influenced by interaction with other receptors. Enhancing our understanding of the protective axis of the RAS would broaden therapeutic possibilities for treating hypertension.
Keywords: inflammation, hypertension, Mas Receptor, heteromerization

Resumen
La hipertensión arterial (HTA) es uno de los grandes problemas de salud de la sociedad actual. Las enfermedades cardiovasculares representan la principal causa de morbimortalidad en los países occidentales. La inflamación juega un rol importante en la patogénesis de la HTA. Las diferentes subpoblaciones de células involucradas en las respuestas inmunes innatas y adaptativas a través de la producción de diversas citoquinas proinflamatorias contribuyen al desarrollo de esta. Uno de los blancos terapéuticos en el tratamiento de la HTA es el sistema renina-angiotensina (SRA). El SRA está formado por dos ejes con efectos opuestos, el clásico presor pro-inflamatorio y el contrarregulador protector anti-inflamatorio. Desbalances en estos ejes favorece una inflamación excesiva, agravando el cuadro hipertensivo. Esta revisión está focalizada en la respuesta que desencadena el eje protector del SRA en la inflamación y cómo esta puede estar influenciada por la interacción con otros receptores. Ampliar el conocimiento del eje protector del SRA abrirá nuevas posibilidades terapéuticas para el tratamiento de la HTA.
Palabras clave: inflamación, hipertensión, receptor Mas, heteromerización

Original received: May 6, 2024. Accepted in the final form: June 7, 2024.

Introduction

Hypertension is a huge health problem that significantly impacts around 45% of adults worldwide, with projections suggesting a substantial rise to 60% by 2025. [1,2] Hypertension is the result of many factors that interact to raise blood pressure and cause end-organ damage. Increased sympathetic nervous systems (SNS) activity, the renin-angiotensin system (RAS), genetic predisposition, endothelial dysfunction, environmental factors, age, among others, contribute to the elevation of blood pressure, leading to cardiovascular damage. [3]

A key factor in blood pressure regulation is the RAS. In the classical RAS, angiotensinogen (AGT) is cleaved by renin to form angiotensin (Ang) I. Ang I is converted by the angiotensin-converting enzyme (ACE) to generate Ang II. Ang II activates both AT1 (AT_1R) and AT2 (AT_2R) receptors. Activation of AT_1R leads to increased blood pressure and SNS overactivity, cardiac hypertrophy and fibrosis, inflammation, vascular remodeling, decreased nitric oxide (NO) bioavailability, and disruption of renal water-sodium balance, among others.[4] This pressor axis is counterbalanced by the protective axis of the RAS which is comprised by ACE2, that catalyzes the conversion of Ang II into Ang-(1-7), Ang-(1-7) and the Mas receptor (MasR) which mediates the vasodilation, NO generation and the reduced cardiac hypertrophy and fibrosis, thrombosis, inflammation, cell proliferation and SNS activation induced by Ang-(1-7). [4,5] The AT_2R also belongs to this protective axis of the RAS since its activation induces similar protective effects as those elicited by the MasR.[6] Thus, the actual view of the RAS is to be considered by two axes with opposing actions (Figure 1). Overexpression of the pressor axis induces hypertension.

Inflammation plays a significant role in hypertension pathogenesis. [1,2,7] Pro-hypertensive stimulus, like Ang II, induces inflammation, aggravating target organ damage and hypertension. [7] This review is focused on the effects of the protective axis of the RAS on inflammation and how such response is influenced by interaction with other receptors.

Inflammation and hypertension

Inflammation influences hypertension development. [3,7] The various subpopulations of cells involved in innate and adaptive immune responses like T cells, monocytes, macrophages, dendritic cells, B cells and natural killer cells, are all implicated in hypertension pathogenesis[8,9] The activated immune cells migrate to target organs such as arteries (especially the perivascular fat and adventitia), kidneys, the heart and the brain, where they release effector cytokines that elevate blood pressure and cause vascular remodeling, renal damage, cardiac hypertrophy, cognitive impairment and dementia. [7-9] Reactive oxygen species (ROS) in antigen presenting cells promote oxidation of fatty acids to form highly reactive isolevuglandin products that covalently modify protein lysines. These altered proteins are antigenic and activate both CD8+ and CD4+ T cells. [5,8,9]

Neoantigens, the NLRP3 inflammasome, increased sympathetic outflow, and a high-salt environment, also contribute to immune cells activation. Sodium entry via an amiloride sensitive sodium channel induces dendritic cell activation, and promotes transformation of human monocytes to a dendritic cell-like phenotype that produce cytokines like interleukin (IL) 6, TNFα and IL-1β and ROS with the subsequent generation of isolevuglandin products thereby exacerbating the progression of hypertension. Extensive preclinical and clinical research supports the notion of AT_1R activation by Ang II playing a significant proinflammatory role. [7,10]

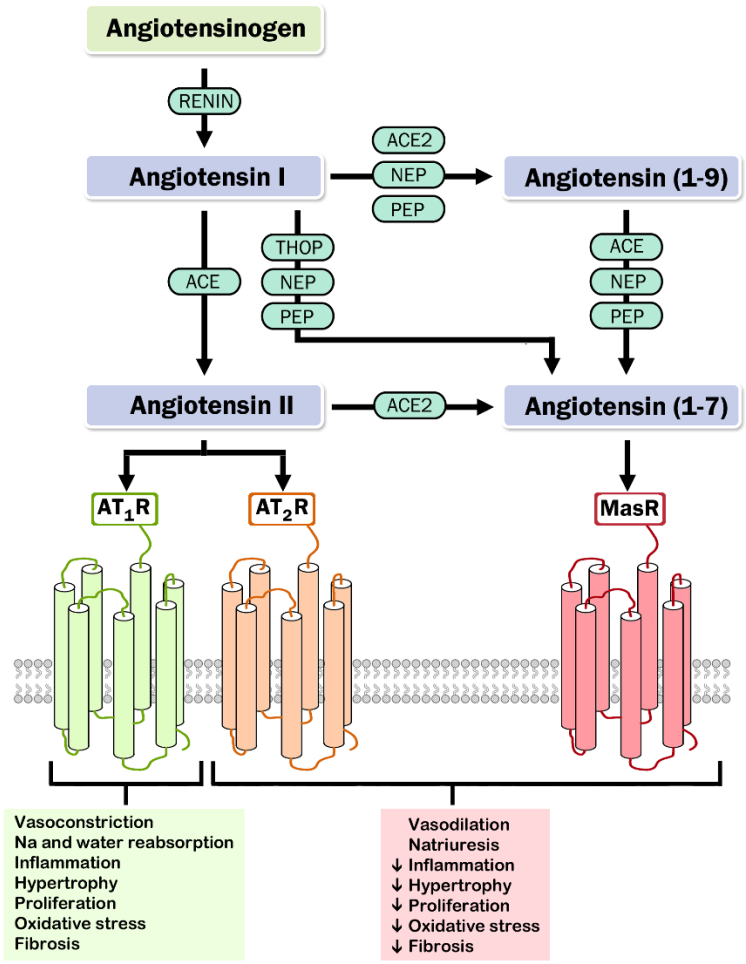

Figure 1. The actual view of the renin-angiotensin system. Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang II, Angiotensin II; AT_1R, Ang II receptor type 1; AT_2R, Ang II receptor type 2; MasR, Mas receptor; NEP, neprilysin; THOP, thimet oligopeptidase; PEP, prolyl endopeptidase.

The protective axis of the RAS and inflammation

Numerous studies have demonstrated that the Ang-(1-7)/MasR axis diminishes proinflammatory cytokine release in experimental models of various inflammatory-mediated human diseases, including atherosclerosis, cerebral ischemia, obesity, chronic kidney disease, liver diseases, and asthma. [11,12,13,14,15] This axis induces macrophage polarization to the anti-inflammatory M2 phenotype, activation of T lymphocytes, reduction in neutrophil influx and cytokine production, increased spherocytosis and resolution of allergic pulmonary inflammatory response [13-16] (Figure 2). MasR-mediated effects on inflammation has been reviewed in a previous number of Physiol. Mini Reviews (*Physiol Mini Reviews, Vol 12 Nº 6, 2019*) and because of space limitation will not be discussed in detail here.

The other component of the protective axis of the RAS, the AT_2Rs, also induces anti-inflammatory responses. AT_2Rs activation triggers the release of numerous cytokines and exerts multiple effects that converge to promote anti-inflammatory actions and prevent maladaptive repair. [17]

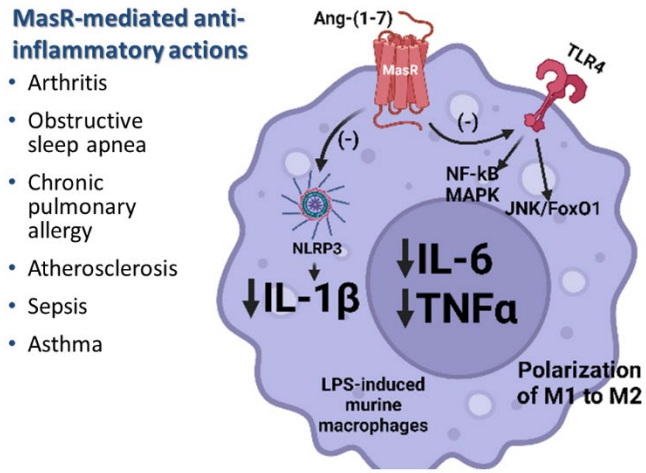

Figure 2. Anti-inflammatory responses mediated by MasR. Abbreviations: IL, interleukin; TNF, tumor necrosis factor; LPS, lipopolysaccharide; NF, nuclear factor; TLR4, toll-like receptor; NLRP3, inflammasome.

Receptor Heteromerization

The AT1R, AT2R and MasR belong to the G-protein-coupled receptors (GPCRs) family.[17] GPCRs can form multi-receptor complexes with the same or different receptor subtype forming homomers and/or heteromers. These complexes exhibit distinct pharmacological properties compared to individual receptor units. [18,19] Thus, heteromerization plays a significant role in shaping receptor function, allowing receptors to display unique expression patterns, ligand-binding characteristics, intracellular trafficking behaviors, biological activities and signaling responses (Figure 3). [19,20,21] This increased complexity enhances receptor signaling networks by introducing diversity, selectivity, and specificity to receptor-mediated signaling processes. [18,20]

To confirm receptor heteromerization, at least two of the following three criteria must be met: 1) demonstration of physical association in native tissue or primary cells, 2) distinct biochemical properties compared to its respective monomers, and 3) loss of heteromer-specific properties upon heteromer disruption. [22]

An intriguing aspect observed in heteromers with significant pharmacological implications is the phenomenon of cross-inhibition. This phenomenon involves a particular antagonist targeting one receptor within a dimer, thereby also inhibiting the signaling of the other receptor in the dimer. Cross-inhibition has been documented for various receptor pairs, including AT2R and MasR, AT2R and the relaxin receptor, MasR and the dopamine type 2 receptor (D2R), or β-AR and AT1R, among others. [23] In this regard, heteromerization of the receptors belonging to the RAS modulates their activity through interaction with other GPCRs, with implications in cardiovascular and neurological disorders. [21] For instance, AT1R-B2R heteromerization heightens sensitivity to Ang II in conditions such as preeclampsia, while AT1R-AT2R heteromerization dampens AT1R-mediated responses. [23] Additionally, heteromerization between AT1R and D2R attenuates the calcium response to Ang II, potentially impacting conditions like dyskinesia. [21,22]

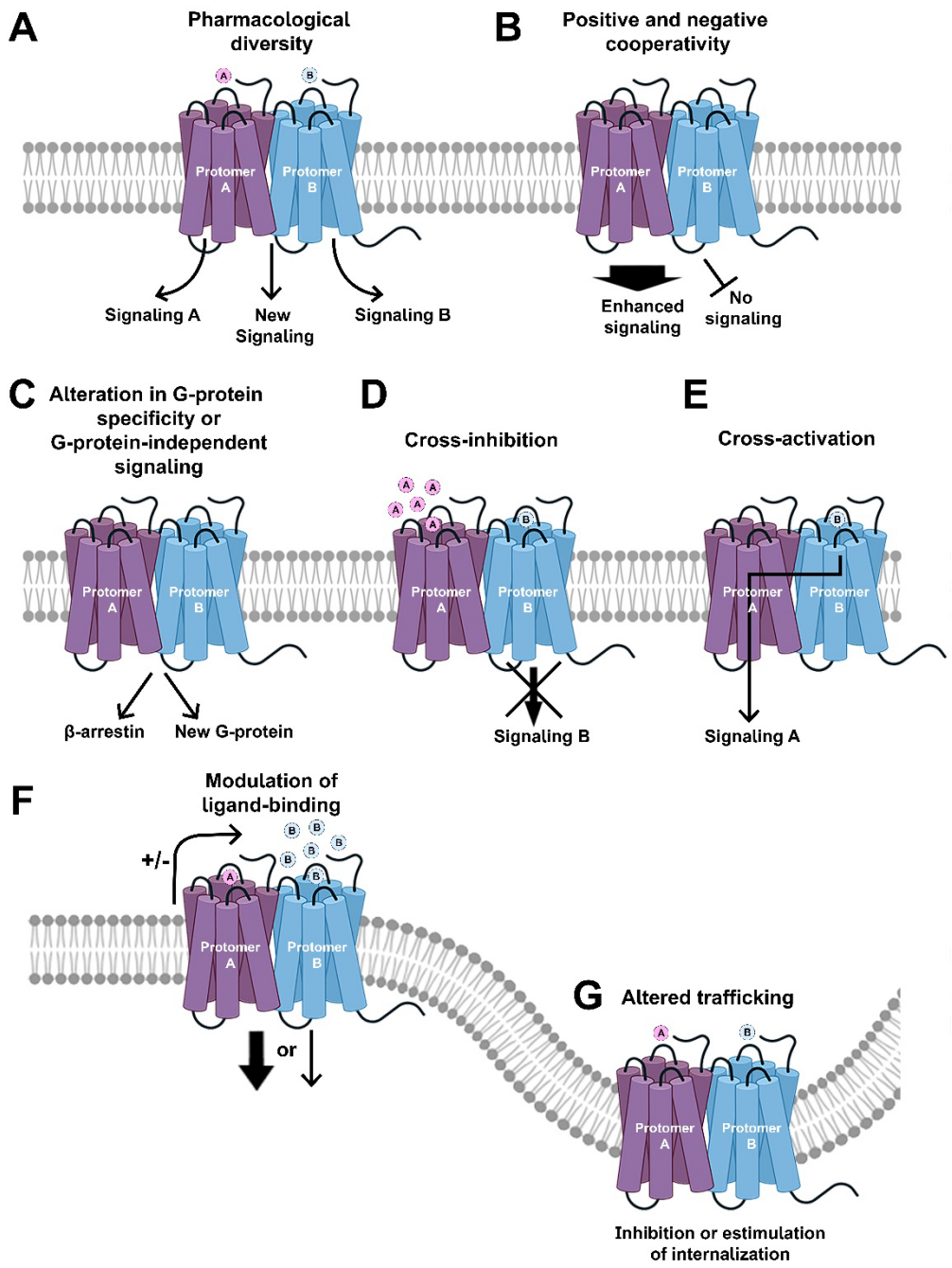

Figure 3. Functional consequences of GPCR heteromerization. Diagram illustrating the primary cellular effects resulting from receptor heteromerization. Heteromerization often introduces novel conformational possibilities, leading to the activation of different downstream signaling pathways compared to individual receptors (A). Ligand binding can exhibit positive or negative cooperativity (B), where the binding of a molecule to one receptor affects the affinity of a second ligand targeting the adjacent receptor, altering signaling efficiency. Heteromerization of G protein-coupled receptors (GPCRs) can cause structural changes near the G protein binding site, potentially influencing G protein affinity, selectivity, or biasing responses toward the β-arrestin pathway (C).
Cross-inhibition (D) is commonly observed in heteromers, where an agonist (negative cross-talk) or antagonist (cross-antagonism) targeting one receptor can inhibit the actions of its interacting partner. Cross-activation (E) is another mechanism resulting from heteromerization, where activation of one receptor's downstream pathway occurs due to agonist-mediated activation of the other. Receptor heteromerization can also alter the ligand binding pocket, changing the affinity of one or more receptors for their ligands (F). Additionally, oligomerization may influence receptor trafficking (G).

Heteromerization of RAS receptors influencing inflammation

- *AT_2R and the MasR*

The physical interaction between AT2R and MasR has been confirmed, showing sensitivity to reducing β-mercaptoethanol, which implies the involvement of –SH groups in cross-linking with a significance of the Cys35 residue of AT2R for heteromerization with MasR. [24,25] Functionally, AT2R and MasR has demonstrated mutual dependence by stimulating NO and promoting a diuretic-natriuretic response in obese rats. Regarding inflammation, AT2R-MasR heteromers induce an elevation of the expression of CX3C chemokine receptor-1 (CX3CR1) mRNA in primary cultures of astrocytes from wild type mice. The activation of CX3CR1 is associated with anti-inflammatory effects, suggesting that the increase in CX3CR1 expression mediated by AT2R-MasR may contribute to the anti-inflammatory effects induced by both MasR and AT2R. [26]

Furthermore, AT2R-MasR is also present in various cell types including human umbilical vein endothelial cells and primary cultures of mice striatal neurons and microglia. This is crucial for brain diseases that show significantly higher levels of brain inflammation in several brain regions, such as Parkinson's disease (PD). [27] In a rat model of PD, AT2R-MasR heteromers are found in the striatum, with heightened expression in the lesioned hemisphere and non-dyskinetic animals treated with l-DOPA. However, the exact significance of this heteromer in PD remains unexplored.

Microglia are the macrophages resident in the central nervous system and key mediators in neuroinflammatory processes. [28] AT2R-MasR has been shown to be present in microglia and to exhibit a negative cross-talk in cAMP and MAPK signaling pathways: blockade of Gi-mediated AT2R function when coexpressed with MasR, and inhibition of MasR-mediated MAPK pathway activation when AT2R is activated. [26]

- *MasR and the AT_1R*

MasR functions as an antagonist to AT1R by blocking the Ang II-induced production of inositol phosphates and intracellular Ca++ mobilization mediated by AT1R. [21] MasR-AT1R heteromers remains unaffected by agonists or antagonists for either receptor. [21] Studies on MasR-deficient mice confirm the significance of this interaction, showing heightened Ang II-mediated vasoconstriction in mesenteric microvessels in MasR-KO mice. Additionally, the MasR-AT1R interaction contributes to Ang-(1-7)'s proangiogenic signaling. Ang-(1–7) contributes to endothelial homeostasis through ERK1/2, eNOS, PI3-kinase, and Akt, which are also associated with AngII signaling through AT1R [29]

MasR-AT1R heteromers are found in primary cultures of mouse striatal neurons, surpassing MasR-AT2R heteromer abundance. [29] They are present in both resting and activated microglia suggesting a role in inflammation. The amount of MasR-AT1R heteromers are similar in resting and activated microglia but higher than in neurons. MasR-AT1R levels increase in the rat striatum under parkinsonian conditions and in animals with dyskinesia due to levodopa treatment. These heteromers show negative cross-talk in cAMP and MAPK signaling pathways in microglia, because cotreatment with agonists induces a lower signal than Ang II. This indicates a negative crosstalk effect in both cAMP and MAPK phosphorylation signaling pathways. [26,30]

- *MasR and D_2R*

Dopamine controls ion transport and blood pressure by regulating the production of reactive oxygen species and the inflammatory response. Essential hypertension is associated with abnormalities in dopamine production, receptor number, and/or posttranslational modification [31]. Studies in mice have demonstrated that global deletion of the D2R and single nucleotide polymorphisms (SNPs) within the D2R gene results in elevated renal inflammation and blood pressure. [31] Activation of D2R induces anti-inflammatory effects through the inhibition of proinflammatory cytokine production. Furthermore, D2R stimulation has been shown to suppress NLRP3 inflammasome activation, a key component in the inflammatory response. [32,33]

The MasR form a heteromer with the D2R which is implicated in anti-inflammatory response[34] These receptors physically interact, resulting in a decrease in IL-6 levels in human macrophages. Notably, the D2R-mediated reduction in IL-6 is prevented upon downregulation of MasR, underscoring the interdependence of the functionality of one receptor on the presence of the other.

Importantly, MasR-D2R heteromers play a pivotal role in facilitating Akt and ERK1/2 activation induced by both receptors. [34]

Concluding remarks

Pharmacological interventions targeting GPCR interactions hold implications for conditions like hypertension, heart failure, and renal dysfunction. Disrupting or enhancing protomer interaction represents a novel pharmacological concept. Overall, heteromerization serves as a mechanism for modulating receptor function and facilitating crosstalk between GPCRs. Understanding the interplay between GPCRs may provide insights into the development of novel therapeutic strategies targeting several inflammatory disorders.

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About authors

Mariela M. Gironacci, PhD. Full Professor. Department of Biological Chemistry, School of Pharmacy and Biochemistry, Buenos Aires University. Principal Investigator of the National Council of Scientific and Technical Research (CONICET). Buenos Aires, Argentina.

My laboratory research has been focused on Mas receptor regulation in physiological and pathological conditions as in hypertension. Mas receptor mediates protective responses elicited by angiotensin-(1-7), a component of the protective arm of the renin-angiotensin system. We also investigated Mas receptor regulation due to heteromerization with others receptors and how this interaction influences its trafficking, affinity, signaling and biological activity. In the last year we have been involved in a project related to COVID-19. We investigated the content of angiotensin-converting enzyme 2, the receptor for the etiological agent of COVID-19, SARS-Co-V2, in subjects hospitalized with COVID-19.