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Controversies in the pathophysiology of arterial hypertension: A narrative review.

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Abstract

Introduction: Purinergic receptors actively participate in the renal alterations in high blood pressure. The elevation of ATP in the renal interstitium activates purinergic receptors, constituting a fundamental pathway in the generation and persistence of arterial hypertension.

Objective of the review: This article is a narrative review that aims to show the importance of new concepts in the pathophysiology of arterial hypertension.

Essential points of the review:

Purinergic receptors are ATP receptors; the more significant the ATP, the greater the purinergic receptors.

Elevated ATP concentrations alter fundamental mechanisms related to blood pressure control, such as the pressure natriuresis mechanism and renal sodium excretion, the regulation of glomerular filtration, and the tubuloglomerular feedback mechanism. The alteration of these mechanisms decreases urinary sodium excretion.

Whether influenced by genetic alterations or induced by vasoconstrictor peptides, a decrease in renal function and tubulointerstitial injury occur before the glomerulus is injured.

The interaction between angiotensin II and purinergic receptors favors the progression of kidney damage.

Conclusion: Kidney damage caused by high blood pressure is critical, so efforts should be made to control hypertension to prevent the progression of damage that leads to kidney failure. To obtain better blood pressure control, developing purinergic receptor antagonists for clinical use is possible.

Keywords:

Arterial hypertension, ATP, Purinergic receptors, Angiotensin II.

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The 20th century was notable for scientific advances in arterial hypertension research. On the one hand, angiotensin II was discovered, which provided invaluable knowledge of the pathophysiology of the disease. On the other hand, the discovery of angiotensin II converting enzyme (ACEi) inhibitors radically changed the future of treating arterial hypertension [1-4]. However, although treatment with ACEis has revolutionized medicine and improved the prognosis of diabetic patients with kidney disease, it has not been possible to prevent the development of cardiovascular complications of uncontrolled hypertension, including kidney failure.

Currently, kidney failure in hypertensive patients is one of the significant causes of morbidity worldwide, surpassed only by that caused by diabetes [5]. The risk factors for developing hypertension include a high-salt diet, junk food, a sedentary lifestyle, obesity, and the stress of everyday life, among others.

The concept of the pathophysiological mechanisms that participate in the development of kidney injury has been modified with the advancement of knowledge. Initially, the hemodynamic theory proposed by Dr. BM Brenner postulated that systemic pressure is transmitted to the glomerulus. This damage is due to the inability of the afferent arteriole to contract and control the pressure that reaches the glomerulus. Although there was hypertrophy and hyperplasia of the arteriole, it was not sufficient to prevent microvascular injury in the peritubular capillary network, with plasma and cells leaking into the interstitium that allowed the development of tubulointerstitial injury [6, 7]. However, inflammatory lesions are observed from the beginning of the disease and are essential for the development of structural lesions in the glomerulus that lead to end-stage renal disease [8]; mild tubulointerstitial injury can cause renal dysfunction and sodium and water retention, which subsequently leads to persistent hypertension [9]. Furthermore, activating purinergic receptors plays a vital role in developing salt sensitivity, as they stimulate the production of vasoactive mediators, such as endothelin-1, exacerbate tubulointerstitial inflammation and decrease sodium excretion [10].

Purinergic receptors

ATP is a fundamental molecule in the body since it provides the energy required to function in various cellular processes. However, this compound has a system of membrane receptors unrelated to energy production [11]. In 1972, Dr. George Burstock proposed ATP as a molecule whose extracellular effects met the criteria for being mediated by receptors. It was later proven that the effects of extracellular ATP occur through activating purinergic receptors [12, 13]. Purinergic receptors are distributed throughout organisms, and they regulate both physiological mechanisms and pathophysiological alterations since they participate in inflammatory and biochemical processes that lead to cell death. The purinergic receptor system is complex. Initially, the P1 receptors activated by adenosine were described; subsequently, the P2 receptors that respond to ATP were classified into two families according to their pharmacological response: P2Xs, which are referred to as P2Rs 1 to 7; P2Xs, which are referred to as P2Rs 1 to 6; and P2Xs, which are referred to as P2Rs 12 and 13. The difference between them is that the P2X receptors are characterized by channels in the cell membrane coupled to ligands (Na+, K-, Ca2+). In contrast, P2Y receptors have seven transmembrane domains and are connected to G proteins [14].

The renal functions of ATP are essential, as ATP participates in regulating kidney mechanisms such as glomerular filtration and tubular transport and has vasoactive effects. On the other hand, the kidney has intrinsic mechanisms that control long-term blood pressure, such as pressure natriuresis, urinary sodium excretion, and extracellular volume regulation, modulated by purinergic receptors [13 – 15].

One of the most important effects of the purinergic system is that it regulates renal vascular resistance so that when the concentration of ATP increases in the extracellular space, it also increases in the renal interstitial fluid, thereby increasing the perfusion pressure of the kidney. [16, 17]. On the other hand, when endothelial cells are stimulated, they produce ATP, as occurs in flow stress due to the activation of P2X4 receptors [18, 19]. Furthermore, the constant increase in ATP modifies the distribution of purinergic receptors that are overexpressed in areas where there is a decrease in tissue oxygen concentration [18-20].

Purinergic receptors in arterial hypertension

Increasing the concentration of extracellular ATP activates purinergic receptors, which are capable of producing arterial hypertension. These receptors stimulate sympathetic tone and the renin-angiotensin system, which modify sodium excretion mechanisms and can produce vasoconstriction of pre- and postglomerular arterioles. P2 receptors are also overexpressed in individuals with already established hypertension [21], as well as in those with angiotensin II-dependent hypertension [22]. Increased expression of P2X7 receptors has been demonstrated in the glomerulus of hypertensive rats transgenic for renin [23] and salt-sensitive Dahl rats [21]. An increase in the expression of P2X1, P2X4, P2X7, and P2Y1 receptors in intrarenal vessels, in the afferent arteriole, and macula previa has also been demonstrated in angiotensin II-dependent hypertension [24, 25]. The importance of purinergic receptors in kidney tissue is because they participate in the regulation of several blood pressure control mechanisms, such as pressure natriuresis [26], autoregulation of glomerular filtration, renal blood flow [27], tubuloglomerular feedback, and urinary sodium excretion [28, 29]. In the angiotensin-dependent hypertension model, it has been proven that purinergic receptors contribute significantly to the progression of renal injury due to hypertension. Indeed, when arterial hypertension occurs, the glomerular microcirculation is modified; afferent and efferent resistance increase, as does the pressure in the glomerular capillary; as a consequence of

vasoconstriction, glomerular blood flow and the glomerular ultrafiltration coefficient decrease, which results in a reduction in total glomerular filtration and per nephron [22, 24].

In arterial hypertension, high concentrations of ATP at the renal level stimulate the proliferation of smooth muscle cells in renal vessels, resulting in hypertrophy and hyperplasia [30, 31]. These conditions favor deterioration of the tubulointerstitium, as infiltration by lymphocytes and macrophages, the proliferation of mesangial cells, the appearance of myofibroblasts adjacent to the glomerular capillaries and capillary rarefaction appear to be associated with hypertrophy of the afferent arteriole [32]. These changes are mediated by activating the purinergic P2X and AT1 angiotensin receptors [33], Figure 1.

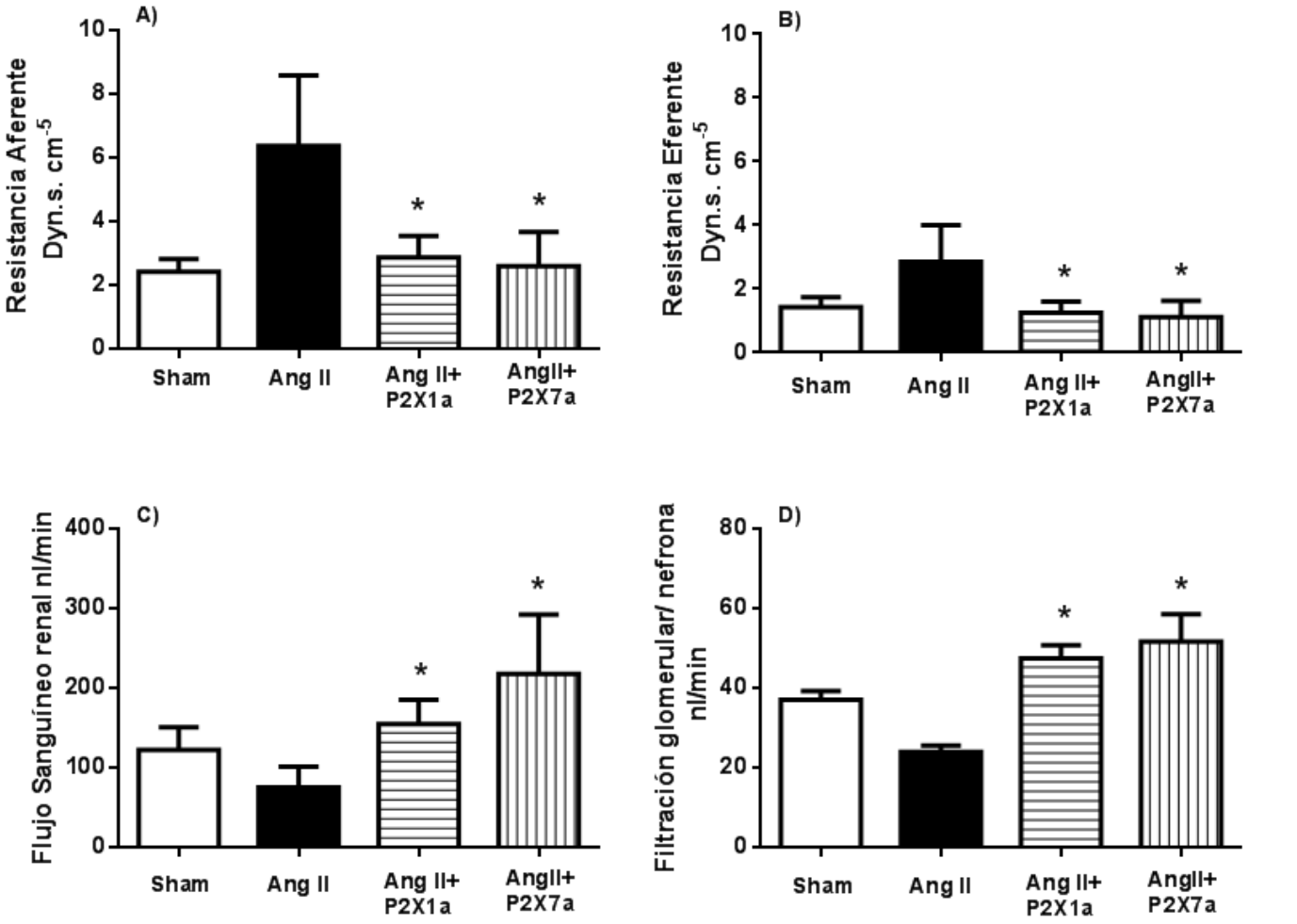

Figure 1.

Renal hemodynamics in rats that received 14 days of Ang II infusion, as well as the specific antagonists of the ATP receptors P2X1 (MRS2159) and P2X7 (408079) (P2X1a and P2X7a) acutely. The groups that received the antagonists had a significant decrease (P >0.05) in afferent and efferent resistance (a and b), which allowed an increase in glomerular blood flow (c). Consequently, glomerular filtration per nephron increased to values similar to regular (d). These results demonstrate that Ang II-induced vasoconstriction can be reversed with a specific ATP antagonist in Ang II-induced hypertension, suggesting an essential contribution of purinergic receptors.

Effect of blockade of purinergic receptors on renal microcirculation in arterial hypertension

Activation of the P2X1 and P2X7 receptors induces the release of vasoactive substances and proinflammatory cytokines that harm renal microcirculation [34, 35]. The P2X7 receptor is responsible for the notable release of cytokines (IL1β, IL18, TNF α, and MCP-1) that can stimulate signaling pathways related to vasoconstriction [21], which is considered proinflammatory [25, 36, 37]. P2X7 receptors are expressed in the smooth muscle of the intrarenal vessels of hypertensive rats [24]; P2X1 receptors are found on endothelial cells and vascular smooth muscle [38]. Consequently, blocking renal vasoconstriction with purinergic receptor antagonists favors renal microcirculation in hypertension because it results in vasodilation [24].

In experiments carried out in our laboratory in the model of angiotensin II-dependent hypertension, when specific blockers of ATP receptors P2X1 and P2X7 were acutely αadministered (MRS2159: English name: pyridoxal-5-phosphate-6-phenylazo-4´-carboxylic acid) and A 438079 (English name: 6-difluoro-4-isopropyloxybenzyl alcohol), decreased afferent and efferent resistance, increased glomerular plasma flow, ultrafiltration coefficient and glomerular filtration to values similar to those of the controls Figure 2 [24]. Graciano et al. administered angiotensin II, an antagonist of the purinergic P2X and P2Y receptors (PPADS, its name in English: pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid), for 14 days. This prevented the trophic effects of angiotensin II on the tubulointerstitium; both the tubulointerstitial infiltrate and the hypertrophy of the afferent arteriole decreased significantly without modifying arterial hypertension or angiotensin II concentrations [32].

Purinergic receptors and inflammation.

An increase in extracellular ATP is a potent stimulus for inflammation associated with ischemia and hypoxia, as well as the production of oxygen free radicals and the processes of necrosis and apoptosis [36, 37, 39]. For ATP to increase in the interstitium, its intracellular release through membrane channels called pannexins and connexins is required [40, 41]. This is usually observed during inflammatory processes, although during the resolution of the process, the local concentration of ATP is generally reduced by the action of ectoenzymes such as apyrase, ATPase, alkaline phosphatase, and ectonucleotidases, which metabolize ATP to ADP and adenosine [42]. However, in experimental arterial hypertension, renal ecto-adenosine deaminase is decreased, which allows an increase in interstitial adenosine [43]; this is important because the balance of vasodilator and vasoconstrictor receptors mediated by adenosine is lost since these receptors also have vasoactive effects. Notably, inflammatory cells express P2X and P2Y receptors, so an increase in interstitial ATP is considered a powerful chemotactic signal [44]. Furthermore, these cells can undergo nonspecific release of ATP in the presence of harmful stimuli, so the release of cytokines and chemotactic factors is stimulated by activating purinergic receptors [42]. Furthermore, the interstitial elevation of ATP modifies the expression and distribution of its receptors and, when associated with the inflammatory reaction, allows the assembly of the nucleotide-binding domain-like receptor pyrin domain containing 3 (NLRP3) inflammasome. [45], which is the essential step for the initiation of a proliferative reaction and the development of fibrosis when hypertension is sustained.

The activation of P2X7 receptors has been linked to the assembly of the NLRP3 inflammasome; however, the mechanism responsible for P2X receptor binding is incompletely known. In this regard, extracellular ATP induces the phosphorylation of proteins that modulate ubiquitination and activate the NLRP3 inflammasome upon increased ATP, as well as the secretion of IL-1 βand caspase-1 in macrophages and dendritic cells [46, 47]. On the other hand, ATP also participates in tissue repair due to its ability to attract phagocytes and dendritic cells [48].

Significantly, some immunosuppressants, such as mycophenolate mofetil (MMF), nonsteroidal anti-inflammatory drugs (pentosan polysulfate), and genetic manipulations, have been associated with a reduction in tubulointerstitial inflammation and kidney damage [49]. This is because treatment decreases the tubulointerstitial infiltration of macrophages that produce NF-κB and inflammatory cytokines (IL1 β and TNF α) that contribute to the assembly of the NLRP3 inflammasome [50]. Treatment with immunosuppressants can prevent elevated blood pressure. For example, when an infusion of angiotensin II is administered for 14 days, followed by a high-salt diet for five weeks, severe arterial hypertension associated with considerable renal vasoconstriction occurs [51]. However, when angiotensin II and mycophenolate mofetil are administered at the same time, the hypertension that develops with a high-salt diet is borderline, and only a moderate elevation of renal resistance is observed in glomerular hemodynamics. Blood flow and glomerular filtration per nephron are maintained at values close to normal; these changes are associated with a significant decrease in tubulointerstitial infiltration [51].

The development of arterial hypertension, salt sensitivity, and activation of purinergic receptors can be simplified as follows. In conditions of hyperactivity of the sympathetic nervous system, exaggerated renin-angiotensin system stimulation, or genetic factors, some stress situations can temporarily elevate blood pressure [9, 52, 53]. When the elevation exceeds the limits of renal autoregulation (>120-130 mmHg in men), an increase in the ATP concentration of the renal interstitial fluid and mild interstitial injury may occur. The transmission of high blood pressure to the peritubular capillaries damages their walls, allowing plasma and leukocytes to escape into the tubulointerstitium; leukocytes promote local inflammation and increase the severity of microvascular and tubulointerstitial injury [54, 55]. These alterations produce focal ischemia, cytokine release, the upregulation of adhesion molecules, and capillary rarefaction, prolonging the inflammatory response [9]. Under these conditions, the effects of angiotensin II, elevated ATP, and tubulointerstitial inflammation are critical factors for the progression of kidney injury [21]. These factors, in turn, increase the sensitivity of the renal mechanisms that regulate blood pressure and the excretion of salt and water, thereby increasing sodium retention [56].

As blood pressure increases, glomerular perfusion improves as hypoxia and tubular ischemia decrease, thereby returning kidney oxygenation and perfusion to values close to normal [27]. At the same time, the elevation of renal blood flow stimulates nitric oxide production, thereby increasing sodium excretion [27]. Blood pressure remains elevated due to the aforementioned tubulointerstitial alterations, but sustaining this elevation is required to maintain normal sodium excretion [56]. Salt-sensitive hypertension subsequently develops, and homeostasis is restored at the expense of hypertension [27]. Therefore, tubulointerstitial injury without glomerular injury is a common condition in the early stages of hypertension. The vascular resistance that initially increases in response to hypertension produces hypertrophy of the afferent arteriole. Despite these adaptive changes, glomerular hypoperfusion and hypertension develop after a specific time and damage the glomerular capillaries, with a subsequent decrease in sodium excretion [54-56].

Conclusions

Uncontrolled systemic arterial hypertension is associated with renal vasoconstriction, which induces hypoxia, oxidative stress, autoimmunity, and inflammation in the kidney. These alterations fundamentally modify the pathophysiological mechanisms that cause salt sensitivity.

For arterial hypertension to develop, a specific combination of factors is required at the renal level: an increase in extracellular ATP and interstitial Ang II, an increase in flow stress, activation of P2X receptors, and infiltration of inflammatory cells in the renal interstitium of the kidney that produce interleukins and growth factors. Alterations in several pathophysiological mechanisms induce renal vasoconstriction in arterial hypertension. Hypoxia, oxidative stress, and inflammation are among the pathophysiological mechanisms that cause salt sensitivity and the progression of kidney injury, which can lead to end-stage renal failure.

Abbreviations

ADP: adenosine diphosphate.
ATP: adenosine triphosphate.
Ang II: Angiotensin II.
ACEi: angiotensin II converting enzyme inhibitors.
IL: interleukins.
MMF: Mycophenolate Mofetil.
P2X: purinergic receptor. Initially, P1 receptors that are activated by adenosine were described. The P2 receptors that respond to ATP are classified into two families according to their pharmacological response: P2Xs, which are referred to as 1 to 7; P2Ys, which are referred to as 1 to 6; and P2Xs, which are referred to as 12 and 13.

Supplementary information

This narrative review has no supplementary materials.

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Does not apply.

Contributions of authors

Rocio Bautista Pérez: Conceptualization, Data curation, Formal analysis, Research, Methodology, Resources
Martha Franco Guevara: Conceptualization, Project administration, Resources, Software, Writing – original draft.

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Availability of data or materials

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Statements

Ethics committee approval and consent to participate

Narrative reviews are not needed.

Consent for publication

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Conflicts of interest

The authors declare no conflicts of interest.

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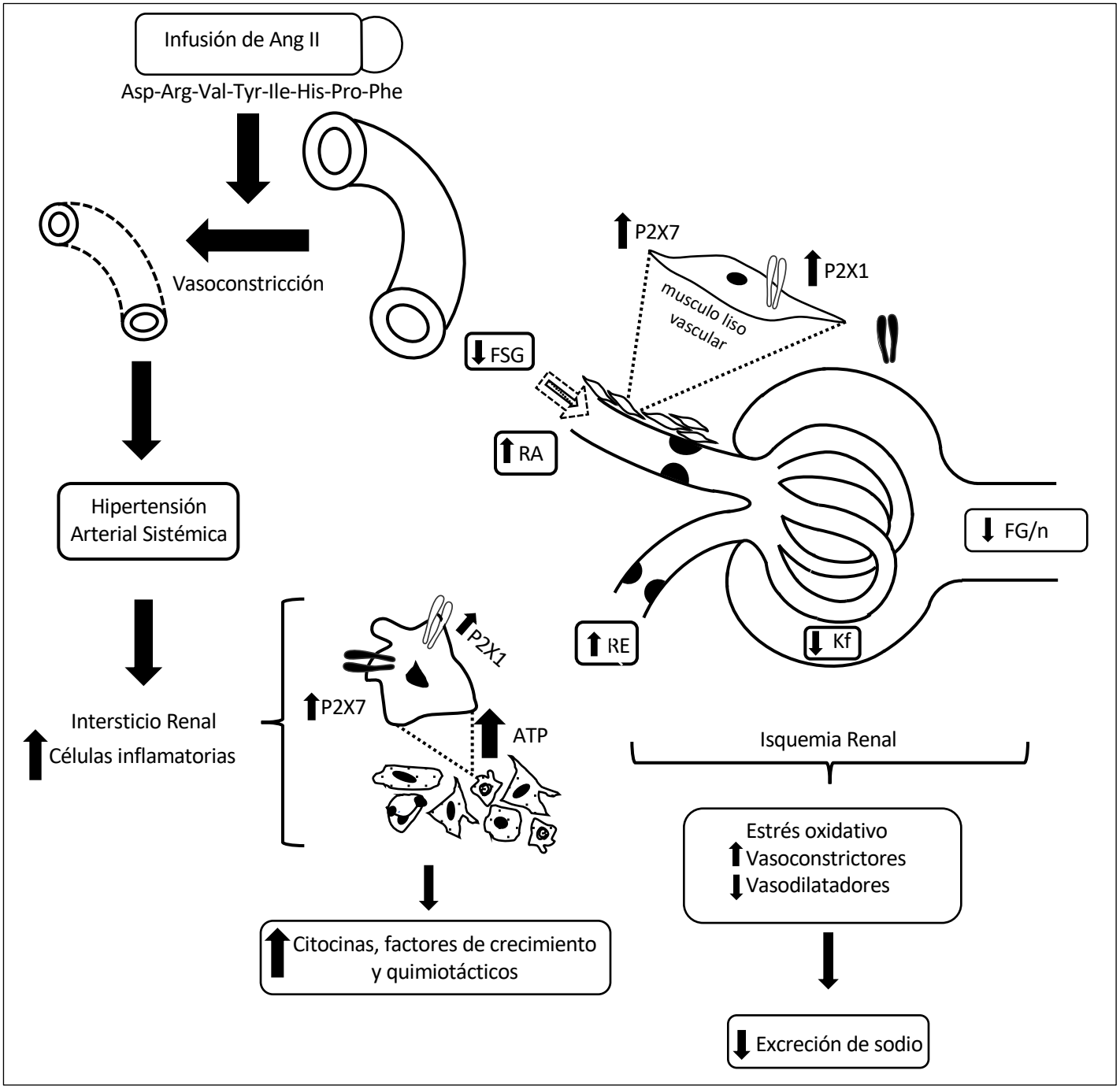

Figure 2.

A schematic of the mechanism that explains the vasoconstriction effect of Ang II infusion for 14 days and the activation effect of the P2X1 and P2X7 receptors. Ang II infusion produces vasoconstriction, systemic hypertension, and increased ATP in the renal interstitial fluid. The smooth muscle cells of the arterioles have P2X1 and P2X7 receptors that, when activated, increase afferent (AR) and efferent (ER) resistance, which decreases glomerular blood flow (GFR). The contraction of mesangial cells results in a decrease in the ultrafiltration coefficient (Kf). These alterations cause a reduction in glomerular filtration per nephron (GFR/nephron). Concomitantly, inflammatory cells of the tubular interstitium induce a more significant increase in ATP and P2X1 and P2X7 receptor overexpression in arterioles and inflammatory cells. Together, these changes promote the production of cytosines, growth factors, and chemotactics; these substances increase infiltration by inflammatory cells and intensify renal vasoconstriction. Renal ischemia induces oxidative stress, with an increase in the local production of adenosine (ADO), angiotensin II (SRA), and sympathetic tone (SNS) and a decrease in nitric oxide (NO). These changes modify the sodium excretion expected when blood pressure rises. FSG: glomerular blood flow.

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