Review

History of vascular reactivity models and their involvement in hypertension pathogenesis

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Summary: Hypertension is a silent and multifactorial disease. Over two centuries ago, the first device to record blood pressure was developed, making it possible to determine normotension and to establish criteria for hypertension. Since then, several studies have contributed to advance knowledge in this area, promoting significant advances in pharmacological treatments and, as a result, increasing survival of hypertensive people. The main models developed for the study of hypertension and the main findings in the vascular area are included in this review. We considered aspects related to vascular reactivity, changes in the population, and action of beta adrenergic receptors in the pathogenesis of hypertension.

Keywords: Hypertension, β-adrenergic receptors, endothelium, vascular reactivity

Introduction

The last few decades have been marked by an increase in risk factors for cardiovascular diseases. The World Health Organization data record about 17 million deaths per year, highlighting 9.4 million due to hypertension complications [1]. However, access to antihypertensive therapy has increased longevity for the hypertensive population [2].

Hypertension development is closely associated with altered vascular reactivity, where any functional impairment in regulating contraction and relaxation of vascular smooth muscle is related to peripheral vascular resistance increase [3]. Thus, vascular tone is the determining factor in peripheral vascular resistance [4], where the endothelium is responsible for controlling blood haemodynamic [5].

The animal models play a crucial role in advancement of medicine in this area and the main models developed for the hypertension study, considering vascular reactivity, are at the centre of this review.

Origin of experimental models of hypertension

The first blood pressure measurement was performed by Stephen Hales in 1733 [6]. This discovery allowed to record the blood pressure of different populations. Thus, it was possible to understand and establish values related to normotension, hypotension, and hypertension. In 1927, after the Hales studies, in which the acute sinoaortic denervation in experimental animals generated elevated blood pressure, the hypothesis that a baroreflex change could lead to hypertension was developed [7]. In 1949, Irving Page presented the Page's mosaic theory, highlighting that hypertension could be a disease of multifactorial origin, which would include genetic, environmental, nervous, haemodynamic, and metabolic aspects [8]. Since then, the scientific community tries to understand the mechanisms regarding the hypertensive disease, by using hypertension experimental models [1]. The most widely studied models are depicted in Table I.

Renovascular hypertension

The first hypertension experimental model of renal origin was developed by Harry Goldblatt in 1934. He demonstrated that reducing blood supply with the aid of a clip in the renal artery would elevate blood pressure in dogs. This model was called Goldblatt Hypertension [9]. The technique consists of unilateral stenosis of a renal artery, maintaining sustained hypertension. There were two possibilities: 1) Application of a clip with contralateral kidney removal, called 1 kidney 1 clip (1K1C), or 2) Application of a clip, but keeping contralateral kidney, called 2 kidneys 1 clip (2K1C) [9].

When the contralateral kidney is maintained, there is a transient increase in blood pressure that restores its nor-

Table I. Animal models and the mechanism of hypertension.

Year	Author	Animal	Mechanism
1934	Goldblatt *et al.* [9]	Dogs	Renovascular hypertension
1946	Selye *et al.* [11]	Rats	Mineralocorticoid-dependent hypertension (DOCA-SALT)
1962	Dahl *et al.* [19]	Rats	Salt-sensitive genetic hypertension
1963	Okamoto & Aoki [14]	Rats	Genetic hypertension (SHR rats)
1964	Krieger *et al.* [22]	Rats	Neurogenic hypertension
1992	Ribeiro *et al.* [23]/Baylis *et al.* [24]	Rats	Hypertension due to chronic nitric oxide synthase inhibition

mal range within a few weeks. However, if the constriction reduces more than 50 % of renal flow, the hypertension could be established for longer according to the degree of obstruction. Furthermore, when the contralateral kidney is removed, the hypertension becomes permanent [7].

This model allowed to link hypertension to the renin-angiotensin-aldosterone system. Whereas the kidney plays a central role in the regulation of long-term blood pressure, aiming to improve this situation, the experimental model of renovascular hypertension has also been widely used [10].

Mineralocorticoid-dependent hypertension (DOCA-SALT)

Developed by Selye in 1946, this model is based on the induction of hypertension by administering agonist deoxycorticosterone acetate (DOCA), with subsequent association with intake of salt and removing a kidney [11]. Excess of mineralocorticoids constitutes an effective method in the induction of experimental hypertension due to excessive sodium and water retention by the renal tubular cells. Consequently there is an increase in blood volume and reduced plasma renin activity, making it a dependent volume model [3].

Vasopressin (antidiuretic hormone-ADH) also plays an important role in this model. It is centrally produced, mainly in the hypothalamus groups of paraventricular and supraoptic neurons in neurohypophysis endings. This hormone is directly involved with the electrolyte balance, and at the same time induces vasoconstriction, which increases water retention by the insertion of aquaporins in end portion cells of the nephron [12]. Studies suggest that administration of sodium along with mineralocorticoids increase blood volume and change vascular reactivity, contributing to the development and maintenance of hypertension [3].

Genetic hypertension

In 1963, Okamoto and Aoki developed an experimental model to study hypertension, which differed from others as it does not require pharmacological or surgical interventions [13]. In this model, animals were genetically selected by genetic inbreeding. In Kyoto Japan, Wistar rats with high pressure provided strains of animals with spontaneous hypertension, dubbing the model *Spontaneously Hypertensive Rats (SHR)* [14]. In 1971, from these animals originated a control strain for SHR, which received the name of Wistar-Kyoto (WKY), as their ancestors were part of the original SHR strain. These animals, despite their descendants, do not develop hypertension and are not congenital strains for SHR. The SHR strains were considered completely pure after 20-fold inbreeding, while WKY was distributed before being considered totally pure. Due to this, the biological variability of WKY may be greater than the SHR [15].

Spontaneously Hypertensive Rat development is considered a reference in hypertension research. The extensive research along with the similar pathophysiology of essential hypertension in humans make the model so important [7]. Test animals develop hypertension at week five and the values to be considered as spontaneous hypertension are between the seventh and 15th week, the plateau occurs between week 20 and 28 [16]. It was observed in this model that the increase in heart rate is prior to the elevation of systolic blood pressure [13].

This model presents peripheral vascular resistance increase, and hence changes in vascular geometry as well as in the cell membrane of smooth muscle cells [7]. Zicha et al. observed less calcium sensitization in the vascular smooth muscle cells, mediated via RhoA/Rho kinase, probably due to the greater influx of calcium by the L-type voltage-dependent calcium channels (L-VDCC) in SHR when compared to WKY controls [17]. However, this link between hypertensive and normotensive should be further clarified.

Salt-sensitive genetic hypertension

Ambard Beaujard (1904) described the relationship between high salt diet and hypertension. Nonetheless, the response to excessive salt intake varies greatly among individuals regarding increased pressure [18]. In 1962 Dahl et al., using sequential breeding techniques in Sprague-Dawley rats, selected animals with the highest and the lowest blood pressure variation for a high-sodium diet. As a result, they obtained two strains, one with significantly increased blood pressure when exposed to a high salt diet, called salt-sensitive (Dahl-SS) and another with a brief blood pressure modification when exposed to sodi-

um overload, called salt-resistant (Dahl-SR). Along these lines, the genetic model of salt-sensitive hypertension was characterized [20].

Hypertension associated with exacerbated salt intake involves multiple factors, including the renin-angiotensin-aldosterone system as well as changes in the vascular dynamic, due to nitric oxide reduction and increased production of superoxide anions [20]. Thus, this model provides important information by contributing to the identification of mechanisms and pathways involved in the development of hypertension [21].

Neurogenic hypertension

The interaction between the neural, central, and peripheral mechanisms in cardiovascular regulation with particular emphasis on the genesis of hypertension also received attention from several researchers.

A major source to this hypertension model is the high sympathetic tone, which was first described by Krieger et al. in 1964 [22], and is one of the most used models for reflex regulation of blood pressure and heart rate study. In this model, elevated blood pressure within 24 hours does not occur due to a vascular or renal defect but due to neural changes involving two sides, the sinoaortic denervation (DAS) and lesions in the nucleus of the solitary tract (NTS), which lead to an exacerbation of sympathetic afferent pathways and consequent blood pressure increase [7, 22].

Hypertension due to chronic nitric oxide synthase inhibition

Hypertension was one of the first diseases associated with decreased bioavailability of nitric oxide (NO) [1], gaining prominence in the development of hypertension models, specifically related to inhibition of NO synthesis [23]. The NO synthesis inhibition occurs by analogues of L-arginine, as N^G-monomethyl-L-arginine methyl ester (L-NAME) through competition with L-arginine by the NO synthase enzyme (e-NOS) [23].

The first description of hypertension in this experimental model was carried out independently by Ribeiro et al. [23] and Baylis et al. [24] in 1992, demonstrating that chronic administration of L-NAME was efficient in developing a persistent hypertension associated with renal damage. This model leads to a rapid deployment of hypertension in the early days, according to L-NAME dose administered, in association with intense peripheral vascular resistance [7].

Ribeiro et al. reported the involvement of renin-angiotensin-aldosterone system as part of this hypertension model, since chronic treatments with angiotensin converting enzyme, or antagonists of AT1 receptors were capable to prevent installation, reversing hypertension, and kidney framework already established [23]. In addition to the e-NOS activity decrease, an oxidative load increase also contributes to the reduction of bioavailability of nitric oxide in this model [25].

With the development of experimental models of hypertension, we realized the unyielding attempt to understand factors that would lead to hypertension development, and we can perceive the importance of vascular integrity for the establishment of blood balance. Thus, the knowledge and understanding of the actions' mechanism of endothelium-derived factors become extremely necessary for the prevention and intervention of hypertensive disease in order to make the development of therapeutic resources and advances in the medical field possible.

Endothelium and vascular tone

Furchgott and Zawadzki in 1980 described the endothelium functions, aside from their structural location, giving rise to one of the most notable achievements of vascular physiology [26]. It has been shown that the relaxation produced by acetylcholine in rabbit aorta and arteriole rings was dependent on the presence and integrity of endothelial cells. They showed that endothelium removal prevented the relaxing action of acetylcholine and concluded that this process involved the release of a key factor for vascular relaxation, called endothelium-derived relaxing factor (EDRF) [26].

In the following years, several research groups were dedicated to characterize EDRF, and several hypotheses on its chemical identity were explored [27]. However, only in 1987, three independent research groups found that EDRF was in fact nitric oxide (NO) [28, 29]. To support this knowledge, Moncada and Ignarro independently conducted a series of experiments; however, the concise evidence of EDRF identity as NO has been proven in 1991 by Moncada et al. Using chemiluminescence, it was validated that endothelial cells, in fact, release NO [30].

These investigations led to the concept that the endothelium was not only a physical barrier, but rather an autocrine, paracrine, and endocrine system of the human organism, metabolically capable of releasing regulatory substances of tone and vascular growth, as well as modulate coagulation and inflammation [31].

In order to consider sensors of haemodynamic changes, the endothelial cells are equipped with highly complex intracellular systems, able to respond both to exogenous and endogenous stimuli, releasing vasoactive substances entitled endothelium-derived constrictor factors (EDCFs) and endothelium-derived relaxing factors (EDRFs) [32]. The interaction between EDCFs and EDRFs on smooth muscle is critical for the regulation of blood flow and blood pressure [33].

Control and maintenance of the tone occur by calcium mobilization in the cells of the vascular smooth muscle, either by opening or blocking these channels, which leads to contraction and relaxation respectively, and intimately depends on the effects produced by EDCFs and EDRFs [34]. Changes in the properties of these factors lead to en-

dothelial dysfunction, contributing to the increase in vascular resistance and consequent tone changing, favouring the hypertensive process [1].

Therefore, scientists began to elucidate the activity and interaction between these substances, aiming to unravel the pathogenesis of hypertensive disease, not only in large vessels such as aorta [1], but also in other beds like splenic movement [35, 36] and microcirculation [37]. In this fashion, many complexes with relaxing factors and endothelial contractile action were synthesized and tested in order to formulate new drugs to aid hypertension treatment [38, 39], starring the importance of substances released by the endothelium.

Endothelium-derived contracting and relaxing factors

Contracting

Among the factors considered endothelium-derived contraction are the endothelins [40], superoxide anions (O_2^-) [41], products derived from the arachidonic acid metabolism such as thromboxane A_2 (TXA_2), prostaglandins H_2 and F_2 (PGH_2 and PGF_2) [42], and angiotensin II [43].

Endothelins

Discovered between 1985 and 1986, three groups showed that the porcine endothelial cells produced a potent vasoconstrictor peptide called Endothelin, subdivided in endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3); however, only ET-1 is expressed in the vascular endothelium [44]. Endothelin-1 exerts paracrine function and its release occurs in the subluminal portion of the cell, acting directly on the vascular smooth muscle [44]. It acts through two receptors: A) On a large scale in vascular smooth muscle cells and in cardiac myocytes; B) in endothelial cells, but it is mainly through the ET-A receptors that ET-1 performs vasoconstriction [36]. It is produced when the endothelium is in a hypoxic situation, i.e. low temperatures or pressurization [45]. However, it is closely related to the pathogenesis of hypertension, correlating increase of constrictor tone for ET-1 and ET-B decrease [44]. Endothelin action leads to increased calcium current through voltage-dependent channels [45]. It acts through the Gi protein which causes the activation of phospholipase C, releasing inositol triphosphate (IP_3) and diacylglycerol (DAG) [43]. The Protein kinase C is activated by IP_3 and DAG and elevates intracellular calcium levels causing smooth muscles contraction [43]. Studies point to a derived relaxing effect of the ET-B endothelin receptor, present in the endothelium, releasing NO and PGI_2 [35, 36].

Superoxide anion

Superoxide anion is considered an EDCF. It is a free radical, with high affinity with NO, and reduced NO bioavailability because it inhibits its action. This is probably the most important mechanism, where oxidative stress influences endothelial function and consequently its vasodilatory effect [46]. The superoxide anion O_2^- reacts with NO, yielding nitrite peroxide ($ONOO^-$), which is highly reactive and damaging to biomolecules, and by the action of superoxide dismutase (SOD), O_2^- is turned into hydrogen peroxide (H_2O_2), and may be converted into water by the action of glutathione peroxidase (GPx) or catalase [47]. The main source of O_2^- is the enzyme complex NADH/NAD(P)Hox, which catalyses the reduction of molecular oxygen by the action of the NAD(P)H as an electron donor, generating O_2^-. This system is a major source of O_2^- in endothelial cells and smooth muscle cells [47].

Cyclooxygenase pathway (COX)

As a result of the release of membrane phospholipids and the subsequent activation of the enzyme phospholipase A_2, the arachidonic acid is formed, which serves as substrate for the enzyme cyclooxygenase pathway (COX) [48]. The prostaglandin G_2 is produced through the COX pathway, which generates prostaglandin H_2 (PGH_2) through the action of a peroxidase [49]. Moreover, it is mediated by tissue-specific isomerases and originates multiple biologically active eicosanoids (prostaglandins and thromboxane) [33, 50].

Among prostanoids that participate in vascular contraction, there is prostaglandin $F_2\alpha$ ($PGF_2\alpha$) and thromboxane A_2 (TXA_2) [33]. Once secreted, they exert their effects via specific receptors: FP, TP, respectively, for $PGF_2\alpha$ and TXA_2 and are coupled to the G protein, and once stimulated, they activate the phospholipase C enzyme that forms IP_3 and DAG, resulting in increased intracellular calcium concentration and consequent vasoconstriction [48].

Angiotensin II

Angiotensin II (AII) is a peptide with a broad spectrum of biological activities, including vasoconstriction [51, 52]. Renal juxtaglomerular cells release a glycoproteolytic enzyme called renin, which acts on a protein derived from the pericentral area of hepatic lobules, called angiotensinogen, and generates the decapeptide angiotensin I [51]. Angiotensin I (weak vascular activity) undergoes hydrolysis by the angiotensin converting enzyme (ACE) originating the active octapeptide: AII [51]. AII is produced in several tissues such as heart, kidney, vessels, adipose tissue, reproductive, and digestive tissue [53]. It integrates a system called renin-angiotensin-aldosterone system (RAAS), which is considered one of the basic systems in the regulation of blood pressure and haemodynamic stability [51].

Its action takes place through activation of its receptors AT_1 and AT_2 [51, 52], where vasoconstriction is promoted by AT_1 receptors, present in vascular smooth muscles [54]. The AT_2 receptors counterbalance the action of AT_1 receptors; however, its expression is considered mild compared to its counterpart [51, 55].

The AT_1 receptor is coupled to a G protein and their activation leads to subsequent activation of phospholipase C, deforming IP_3 and DAG with increased intracellular calci-

um concentration and vasoconstriction [56]. Angiotensin II also releases aldosterone, which promotes secretion of K^+ and consequent retention of Na^+ and water [52]. Hyperactivation of RAAS is linked to high blood pressure, highlighting the RAAS products as the main target for the antihypertensive therapies [52, 54, 57].

Relaxing

Prostacyclin (PGI_2) [58, 59], the endothelium-derived hyperpolarizing factor (EDHF) [60], and nitric oxide (NO) all share relaxing effects [26].

Prostacyclin

Discovered by Vane and Moncada in 1976, PGI_2 is considered an important eicosanoid that triggers vascular relaxation [33]. Released in response to shear force or shear stress, it is synthesized in endothelial cells from the release of arachidonic acid. Once free in the plasma, it is metabolized by COX and then undergoes the action of a prostacyclin synthase, generating PGI_2 [33, 35, 61].

PGI_2 is lipophilic, it goes through the membrane of endothelial cells and binds to the IP receptor, coupled to the G protein located in the plasma membrane of smooth muscle cells. Thus, it induces activation of adenylate cyclase enzyme, increasing the cAMP concentration, then activation of cAMP-dependent protein kinase (PKA) via signal transduction relaxes smooth muscle cells [33]. In vascular smooth muscle cells, there is an activation of K^+ channels sensitive to ATP, which leads to output of calcium of cytosol and hyperpolarization of membrane. This phenomenon inhibits the contractile machinery and hence leads to relaxation of smooth muscles [43].

Endothelium-derived hyperpolarizing factor (EDHF)

Endothelium produces a relaxing factor that does not alter cAMP and cGMP levels, but leads to membrane hyperpolarization of vascular smooth muscles and is resistant to COX and nitric oxide synthase inhibitors. It was first described in 1987 and named endothelium-derived hyperpolarizing factor (EDHF). Its action is mediated by the action of K^+ channels by Na^+/K^+ activation, K^+ATPase channel sensitive or by calcium of small and intermediate conductance (SK_{Ca} and IK_{Ca}). Its vasodilator effect is higher in resistance vessels than in large arteries [33].

Nitric oxide

Nitric oxide (NO) is one of the most important endothelium-derived relaxing factors and plays a crucial role in vascular homeostasis [33]. The NO synthesis in the vascular endothelium is characterized by two phases. At first occurs hydroxylation of one of the guanidinium nitrogens from L-arginine, generating NG-hydroxy-L-arginine (NHA). This reaction uses NADPH and oxygen (O_2), and is catalysed by the endothelium NO synthase enzyme (NOS3 or e-NOS). The second stage consists of the conversion of NHA into NO and citrulline, using flavin adenine dinucleotide (FAD), mononucleotide flavin (FMN), and tetrahydrobiopterin (BH_4) as cofactors in the reaction [5].

The e-NOS is conveniently anchored to the membrane of endothelial cells, which favours the presence of large amounts of NO near the muscle layer of the vessel and circulating blood cells and is regulated by calcium-calmodulin [62].

Due to its small size and its lipophilic characteristic, once produced by the endothelial cell, NO diffuses quickly into the smooth muscle, interacting directly with the haem iron of the guanylate cyclase (GC) enzyme, activating it (GCa). GCa catalyses the output of two phosphate groups of cyclic guanosine triphosphate molecule (GTP) resulting in the formation of cyclic guanosine monophosphate (cGMP). Then, cGMP modulates the protein kinase G, which activates myosin phosphatase of light chain and results in dephosphorylation of myosin of the smooth muscle. This process leads to vascular relaxation by annulment of tonic contraction of the smooth muscle [63].

The vascular smooth muscle relaxation provided by NO also occurs due to the decrease in the concentration of intracellular Ca^{2+}, which is resulting from the direct reduction of Ca^{2+} transport into the cell, sequestration of Ca^{2+} excess from the intracellular fluid into the sarcoplasmic reticulum, by inhibiting the Ca^{2+} release of the sarcoplasmic reticulum, and by reducing the sensitivity of interaction between Ca^{2+} and actin and myosin myofilaments [64].

Adrenergic interaction and hypertension

The sympathetic nervous system plays an important role in controlling blood pressure, influencing the pathogenesis of hypertension [65]. The endothelium and the smooth muscle receive innervation from sympathetic nerve fibres, which perform catecholamine action (noradrenaline and adrenaline). They act through adrenergic receptors present in the vascular bed, directly affecting the vasomotor tone [66]. Adrenergic receptors have been described by Ahlquist in 1948, proposing a division into two broad categories α and β [67]; and then rearranged into subtypes $\alpha_1\alpha$, $\alpha_1\beta$, α_{1D}, $\alpha_2\alpha$, $\alpha_2\beta$, α_{2C}, β_1, β_2, and β_3 [34, 65, 68].

The participation of β-adrenergic receptors in the development of hypertension received great attention by the community, since this class of receptors is present in the endothelium and smooth muscles of blood vessels as well as in the heart [65].

The knowledge about this disease as well as the pharmacological advances in the development of antihypertensive drugs, comes from the study of the structure and function of β-adrenoceptors [69]. β-adrenergic are receptors of seven transmembrane domains, which directly interact with G protein and are phosphorylated by the kinase family (GRKs), which play a regulatory role both in the signalling pathway and in the receptor function [70].

Considering the catecholamine's power range, the beta adrenergic receptors have been subdivided into the cardiovascular system in β_1, prevalent in the myocardium, and β_2, predominant in smooth muscles and the skeletal [71]. After, the subtype β_3, traditionally known as a modulator of lipolysis in adipose tissue, was considered as a regulator of vasomotor tone, along with β_1 and β_2 [72]. In 1989, Kaufmann demonstrated a subtype of β-adrenoceptor, different from the others, proposing the idea of an atypical receptor, called β_4. However, it has been found that this group of receptors was just another conformational state of β_1 that had a low affinity site to agonists and conventional antagonists [73].

Although there is a predominance in the receptor β_2 on vascular smooth muscles [71], it is already known that all subtypes of adrenergic β receptors participate in vascular relaxation, thus influencing the control of blood pressure [66, 72]. A commitment to the balance between endothelial response and receptor signalling β-adrenergic can contribute to increased vascular resistance, resulting in hypertension development [72].

Receptors β_2-adrenergic may act in association with stimulatory G protein (Gs), and also inhibitory G protein (Gi) by distinct mechanisms. Through Gs stimulation, the β-adrenergic receptors activate the adenylyl cyclase (AC), resulting in cAMP production, and subsequent PKA activation, which culminates in a decrease in intracellular calcium levels, resulting in vascular relaxation [65, 71]. When Gi protein is active, it acts through PKA phosphorylation, a negative regulatory function occurs and conse-

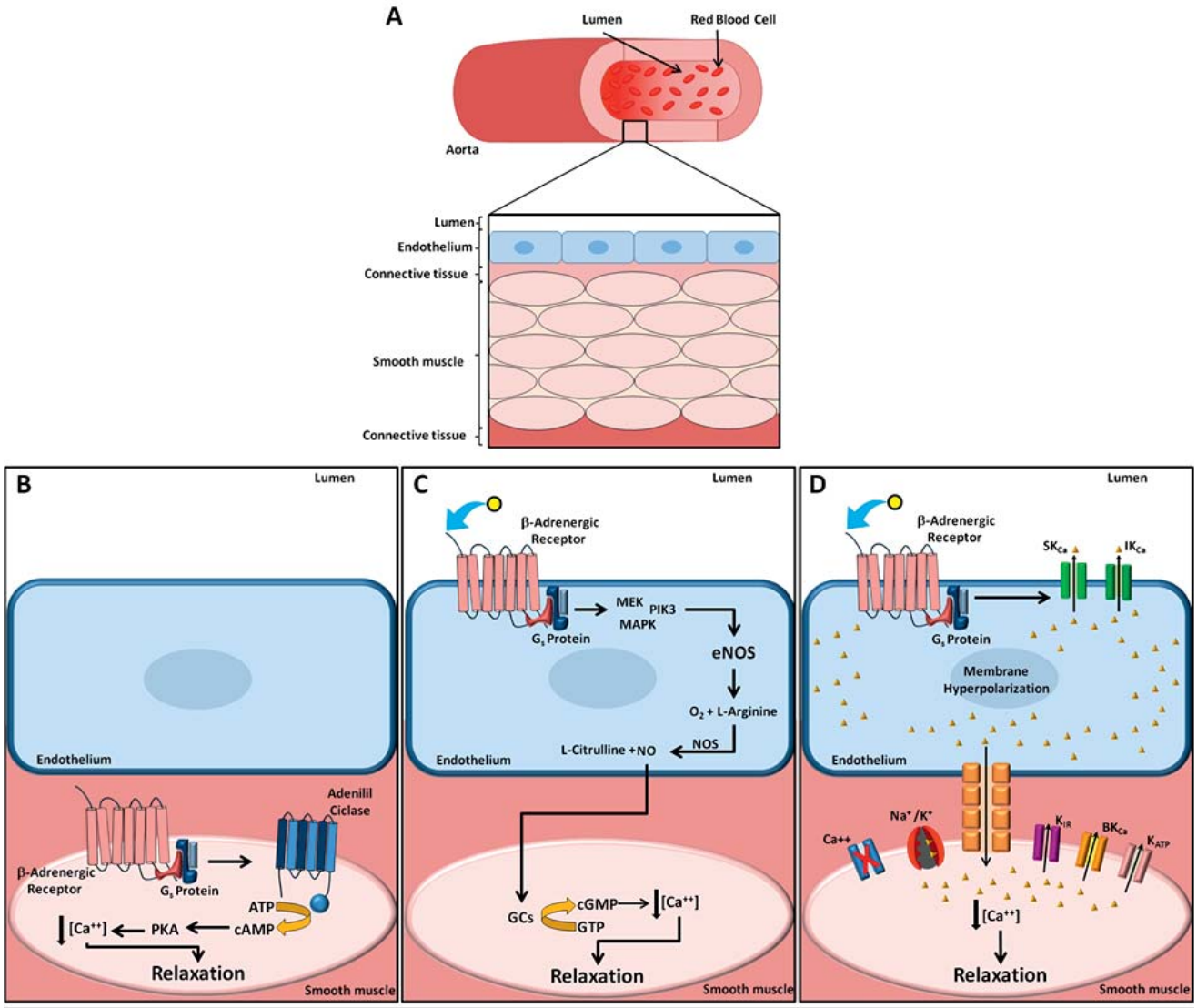

Figure 1. Mechanism of action of β-adrenergic receptors. (A) Classical route of activation of β-adrenergic receptors by interaction with G protein with activation of adenylate cyclase and cAMP production with subsequent activation of PKA, leading to reduction of intracellular calcium with consequent relaxation (B) Activation of β-adrenergic receptor and consequent key proteins activation, leading to activation of eNOS, formation of nitric oxide (NO), which in turn activates the Guanylate Cyclase soluble (GCs) thereby causing conversion of GTP to cGMP resulting in reduction of intracellular calcium concentration of smooth muscle (C) Activation of β-adrenergic receptor resulting in the opening of K+ channels activated by calcium in the endothelium and subsequent opening of K+ channels and activation of pump Na+/K+/ATPase, generating hyperpolarization in smooth muscle cell followed by closing voltage-gated calcium channels, leading to loss of affinity between Ca2+ and calcium-calmodulin complex, resulting in decrease of phosphorylation of myosin light chain kinase (MLCK), all routes resulting in vascular relaxation.

quently receptor desensitization, causing receptor down-regulation [74].

Much has been discussed about the promiscuity of receptor β_2 adrenergic and its cardioprotective effect, and in 2013, Robert Letkowitz received the Nobel Prize for his research and characterization of adrenergic receptors and their clarification on the kinase receptors, G protein-coupled [70].

Receptors β-adrenergic can also exercise their regulatory role of vascular tone by enabling small and medium conductance sensitive potassium channels to Ca^{2+} (SKca/IKca), resulting in first instance hyperpolarization in endothelial cell, which consequently, with the aid of myoendothelial gap junctions, activate opening of K^+ channels, as well as of the pump Na^+/K^+/ATPase in the smooth muscles, causing hyperpolarization of smooth muscle cells, allowing the efflux of K^+ to the extracellular medium. Along with this phenomenon occurs the closing of voltage-gated calcium channels, thereby reducing the interaction of the Ca^{2+}/Calmodulin complex and phosphorylation of myosin light chain, resulting in a relaxing response [34, 71]. Another possibility of relaxing response by activation of β receptors lies in the NO/cGMP pathway. The mechanism involves the participation of the mitogen-activated protein kinases (MEK), MAPK (p42 and p44), ERK1/2 as well as the route of phosphatidylinositol 3 kinase(PI3K), which leads to e-NOS activation, resulting in the production and action of NO , involving the subtypes β_1, β_2, and β_3 acting in smooth muscle cells [65, 75]. Action mechanisms involved in β-adrenergic response are illustrated in Figure 1.

The hyper responsiveness association of β-adrenergic pathway in triggering hypertension has not been fully elucidated; however, it is known that deficiencies in the ability of β-adrenergic responsiveness cause global imbalance between EDCFs and EDRFs, a characteristic of hypertensive condition. The scientific community has endeavoured to clarify the regulation exercised by the receptors β-adrenergic and hypertension models have been used to elucidate the molecular actions performed by these receptors [65].

Promising effects

The existence of this variety of models for the study of hypertension not only contributed to the progress in building the mosaic of knowledge, as quoted by Page in 1949, but actually helped the advance in different antihypertensive therapies. Briasoulis et al. in 2013, published a meta-analysis examining data from 59,285 control patients and 55,569 hypertensive patients, undergoing different therapies [2]. The average age of patients in treatment was 71 years. This study demonstrated that different antihypertensive therapies with the same blood pressure reduction have similar effects on cardiovascular protection [2]. Thus, the correct therapy that restores blood pressure to ordinary values may bring great benefits to the longevity.

Conclusions

The development of different models of hypertension led to evolution of the cardiovascular science, highlighting the fundamental importance of the interaction between endothelial cells and their contractile and relaxing factors in the development of hypertension. Therefore, due to these significant discoveries, the knowledge in the medical field was extended, resulting in improvement of treatments that surround the hypertensive disease.

The challenges are constant, however, studies that clarify the mechanisms of action surrounding hypertension are extremely relevant and thus bring new perspectives to the treatment of hypertension. Improvement evidences in the quality of life and longevity of hypertension patients are definitely a result of the dedication of numerous researchers and their magnificent experimental models, still indispensable to science.

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