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Hypertension and Renin-Angiotensin System

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1. Introduction

The renin-angiotensin system (RAS) participates in numerous biological activities. Among these is the pathophysiological mechanisms of hypertension, congestive heart failure, myocardial infarction, diabetic nephropathy and inflammatory disorders. These pleiotropic effects led to the development of new therapeutic approaches to inhibit the actions of this system. This chapter aims to relate the inflammatory process with the RAS thus focusing on the effects of antihypertensive drugs in the therapeutic and / or prevention of pathophysiological conditions. Also discussed in this chapter also the pharmacodynamic of ACE inhibitors, ARB inhibitors and Direct Renin Inhibitors, as well as a review of the RAS.

For a better knowledge of the system, it is necessary to first discuss the history of RAS components and focusing on general biochemistry, cell biology in its overall effects.

2. Renin-angiotensin system

The RAS is classically known as a circulatory system or hormone that regulates blood pressure and homeostasis of electrolytes and fluids. This classic study is originated from 1898 when Tiergersted and Bergman found that the kidney contained a pressor substance, through non-purified salt extracts, which was called renin. This discovery came only to attract attention with Goldblatt et al in the twentieth century in 1934 when they demonstrated that the constriction of the renal arteries producing persistent hypertension in dogs due to reduction in vascular area with a consequent increase in strength and blood pressure (Goldman and Gilman, 2007). Six years later he declared that the renin was actually a protein that acted on a substrate in plasma. The name of this substrate for 20 years was controversial, as two groups of researchers, one from Argentina and other U.S. called them differently. The first group was called the substrate of *hipertensin* and the second *angiotonin* until these names were changed to *angiotensin*, the true pressor material. The precursor of this peptide was called angiotensinogen. Therefore, the time had an idea this simplified system, Figure 1.

In the 50's has been identified two forms of angiotensin, respectively called of angiotensin I and II. The first would be a chain of 10 peptides, hence the term decapeptide. In contrast, the second would be formed by cleavage of two peptides of angiotensin I to form an octapeptide. This cleavage occurs through the participation of an enzyme located on the luminal surface of endothelial cells of vascular system known as Angiotensin Converting

Enzyme (ACE). In the overview of the peptide angiotensin II is more active, that is, angiotensin II that has the main vasoconstrictor effect. Thus by mid-50, the overall picture of this system was extended by both the description of the two angiotensins, and by the observation that this system RAS concurrently regulated secretion of aldosterone. Based on this knowledge that was acquired, the 70 and 80 was an improvement on the findings of these polypeptides that interfere with components of the RAS, is directly inhibiting the release of renin, or ACE, and angiotensin receptor antagonists. Anyway, these findings allow to the present day an increase in quality of life, these compounds being the main drug involved in the treatment of hypertension, congestive heart failure, diabetic nephropathy, myocardial infarction, more recent studies show the effects of these in inflammatory disorders. To understand this 'fine' relationship between RAS and inflammatory process, it is to reading the components of this system.

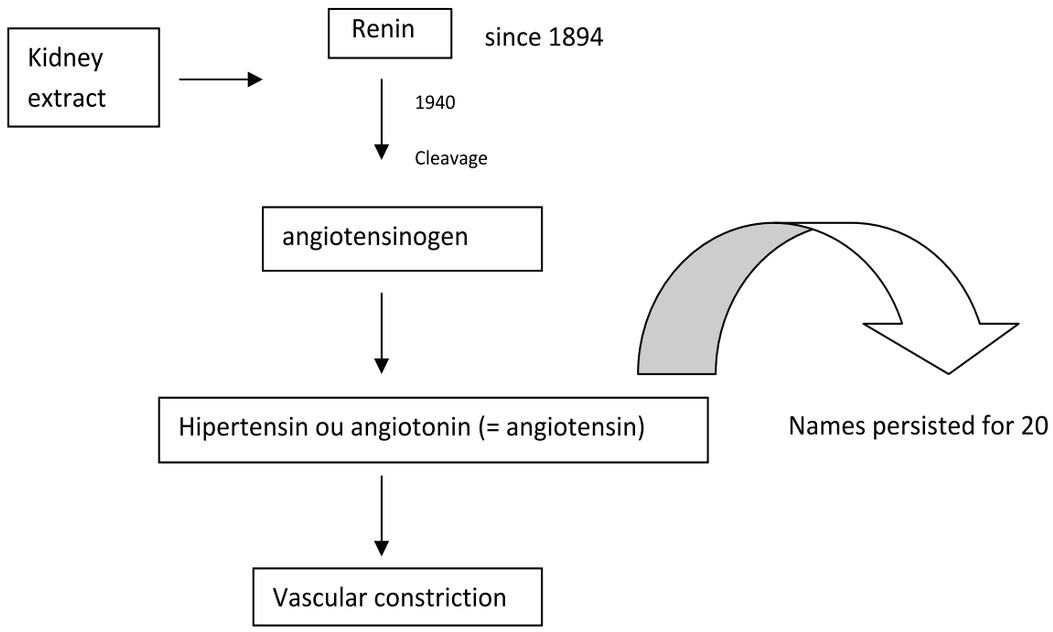


Fig. 1. Diagram showing the evolution in a simplified manner on the physiology of RAS. [Figure made by Barros, RS - 2011].

3. Renin angiotensin system components

Renin: It is the major protease able of determining the rate of production of angiotensin II. Renin is produced, stored and secreted in so-called juxtaglomerular cells, cells that are circulating in the renal artery, present in the afferent arterioles, ie, the infiltrating *glomerulus* in promoting renal perfusion in this region. The release of renin is done through a process called as exocytosis. The main substrate of this aspartyl protease is an α2 - globulin stock, ie, angiotensinogen that is secreted by hepatocytes. Regardless, the renin, which cleaves peptide bonds aminoterminal tail of the angiotensinogen (Leucyl-leucine in mice and rats) and (Leucine-valine in humans), leading to angiotensin I, is an active renin. Thus the synthesis of this protease is done in stages. The active form that contains 340 amino acids. It is synthesized as a pre-pro-enzyme with 406 amino acid residues, soon after, this precursor is processed and thus generates a pro-renin, which is a more mature, but no activity. Soon

after this process pro-renin is activated by an enzyme not yet characterized, but cleaves 43 amino acids of the aminoterminal tail, thereby generating active renin. The secretion of renin by the juxtaglomerular cells (CJG) is controlled mainly by three ways: two act locally in the kidney and third acts indirectly through the CNS that releases norepinephrine from noradrenergic nerves of the kidney. The macula densa is a mechanism that controls the release of renin. It is a complex mechanism that relies on receptors, cyclic adenosine monophosphate (cAMP) and also through prostaglandins. In general, the macula densa is located adjacent to the CJG and is composed of columnar epithelial cells. When any change occurs in the flow of NaCl present in the macula densa cells release chemical signals that the CJG will inhibit or stimulate renin in the event of an increase or reduction of NaCl respectively. These signals via macula is mediated by both adenosine and prostaglandin by the first of which operates in the increase of NaCl and the second reduction. Regardless of which protein will act (adenosine or prostaglandin), the fact is that the answer to these is through the binding of these G protein coupled receptors, which will promote a signal dependent on the cellular second messenger (cAMP). Thus while acting within the A1 adenosine receptor adenosine inhibits renin release, while the prostaglandin stimulates.

The second mechanism that controls the release of renin is intrarenal baroreceptor pathway. This mechanism is regulated by raising and lowering blood pressure in pre-glomerular vessels, and thus are regulated by mechanical phenomenon. This mechanical modulation causes CJG inhibit or stimulate the release of renin. Moreover, the increase or reduction in renal perfusion pressure may inhibit the release or renal prostaglandin which act in part via the intrarenal baroreceptor.

Finally, the third mechanism is called via the beta-adrenergic receptors. In this case, regulation occurs via the CNS. After the release and action of this neurotransmitter norepinephrine from postganglionic sympathetic nerves occurs when it binds to beta-adrenergic receptors stimulating the sympathetic pathway and consequently the secretion of renin by CJG.

These three mechanisms of regulation of renin secretion are involved in a physiological network, explained below:

1. The increased release of renin leads to increased release of angiotensin II. This in turn binds to AT1 receptors in the CJG. This binding leads to inhibition of renin secretion in a mechanism known as short feedback loop.
2. In addition to angiotensin II also leads to an increase in blood pressure by binding these AT1 receptors. In increased pressure leads to a reduction in renin secretion through the action of high pressure baroreceptors, increased pressure from pre-glomerular vessels and reduced pressure natriuresis (drop in reabsorption of NaCl). This mechanism of reduction of renin secretion via increased blood pressure arising from the effects of angiotensin II is known as negative feedback loop long.

Angiotensionogen: It is important to a globular protein, has a (MW = 55,000 to 60,000) and is the main substrate of renin. The angiotensinogen is synthesized in the liver, although it may have also made their transcription in adipose tissue in the CNS and kidney. There is a very close relationship between the synthesis and secretion of angiotensinogen by stimuli such as inflammation, insulin, estrogens, glucocorticoids, thyroid hormone and angiotensin II, ie, all these stimuli increase the synthesis and secretion of dodecahydrate peptide. There

is a strong relationship between the amount of circulating *angiotensinogen* in plasma and increased blood pressure, so the use of oral contraceptives containing estrogen lead to an increase in serum angiotensinogen, thereby resulting in an elevation of blood pressure. At this point becomes more clear also the strong relationship with the inflammatory process. We have seen that directly interferes with the prostaglandin release of renin, ie, prostaglandins increase the secretion of this hormone by binding to adenosine receptors.

Angiotensin Converting Enzyme (ACE): ACE is a glycoprotein ecto-enzyme and that in addition to cleaving angiotensin I to angiotensin II forming this ecto-enzyme can also inactivate bradykinin, because ACE is very nonspecific and can cleave dipeptide units with many amino acid substrate. Therefore, the ACE inhibitors such as captopril and lisinopril, for example, are able to increase bradykinin and reduce angiotensin II. The rapid in vivo conversion of angiotensin I to II occurs through the action of ACE that is present on the luminal surface of endothelial cells throughout the vascular system. In addition to these effects of ACE some studies show the existence of a carboxypeptidase-related enzyme called ACE2 is capable of cleaving angiotensin I into (angiotensin 1-9) and angiotensin II (angiotensin 1-7). This enzyme is not inhibited by classic ACE inhibitors. Its physiological importance is not yet clear.

4. The renin-angiotensin system and its relationship with pathophisiology hypertension

The pathophysiology of hypertension is defined as a lasting elevation of blood pressure to ≥ 140/90 mmHg, as this procedure was used because most individuals with this pressure range belong to risk group cardiovascular disease and hypertension arising from the medical attention they deserve. This disease is like the most common cardiovascular disease and its prevalence increases with age.

The RAS participates as a key player in regulating blood pressure in both long and short term. This happens because the increase, even in modest concentrations of angiotensin II leads to an acute elevation of blood pressure. To get an idea in terms of values to angiotensin II is about 40 times more potent than norepinephrine and effective concentration (EC50) to angiotensin II acute elevation of blood pressure is approximately 0.3 nmol / l. In the presence of angiotensin II administered intravenously pressure rises in a few seconds and after a few minutes this reduces the normal rate. This effect is known as immediate pressor response is due to a rapid increase in total peripheral resistance. This increased resistance is a response that maintains blood pressure in the presence of an acute hypotensive response. Although the direct effects of angiotensin II on cardiac contractility and heart rate indirect in the rapid rise in blood pressure leads to activation of the baroreceptor reflex, and in a negative feedback, this occurs with the reduction of sympathetic tone and increase vagal tone.

On the other hand, there is a slow pressor response, which also occurs by the action of angiotensin II. Response to this pressure is stabilized for a long time. This slow pressor response is most likely due to reduced renal excretion function, causing an increase in fluid retention and salt and, with increasing pressure quently. Associated with these renal effects, angiotensin II in this response also induces the synthesis of endothelin-1 and superoxide anion, which can contribute to this type of slow pressor response. Other classical effects of

angiotensin II on the pathophysiology of hypertension is the morphological alteration of the cardiovascular system, causing hypertrophy of cardiac and vascular cells, and increase the synthesis and deposition of collagen by cardiac fibroblasts.

5. Antihypertensive drugs and its relationship to inflammation

As discussed previously classicaly, the rennin-angiotensin system (RAS) has been considered a hormonal circulating system. The so-called systemic or circulating RAS plays a crucial role in the maintenance of blood pressure and electrolyte as well as fuid homeostasis15. This is mediated through its constrictive actions on vascular smooth muscle and by its influence on aldosterone secretion from the adrenal cortex, electrolyte transport in kidney, and on thirst as well as sodium appetite in the brain. In addition to its actions on the cardiovascular, renal, and nervous system, the expression of local RAS components in tissues such as the brain, kidneys, adrenals and gonads has led to the proposition that these components may either potentate systemic functions, or have entirely separate activities meeting the specific needs of these individual tissues.There is accumulating evidence that changes in tissue/organ-specific RAS may be associated with the pathophysiology of the respective tissue/organ functions (Ip et al., 2003).

The final goal of the RAS is the angiotensin II production that acts through the interaction with two pharmacologically defined receptor subtypes, namely type 1 (At1) and type 2 (At2) that are distributed in numerous target tissues and organs like pancreas, for example (Chan et al., 2000).

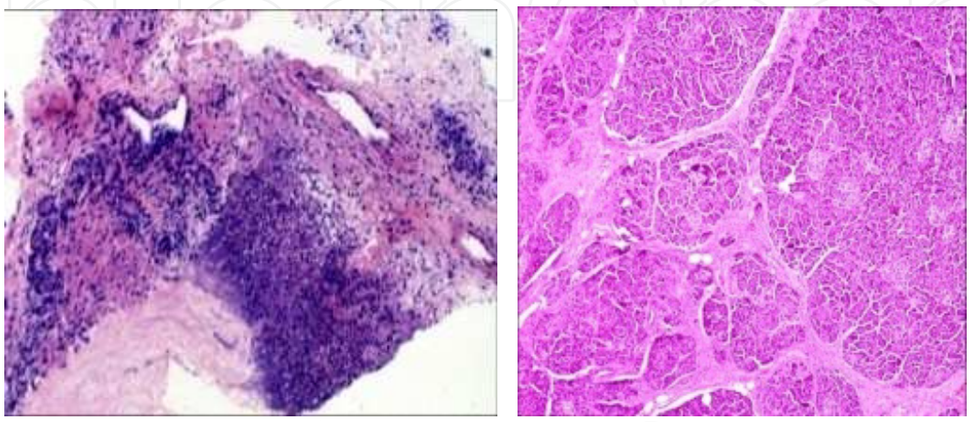
Some studies show that AT1 and AT2 receptors when activated by angiotensin II may lead to tissue that expresses inflammatory responses develop. This is the case of acute pancreatitis, which expresses the receptor AT1a more significantly than the receiver AT1b. In contrast, the AT2 receptor is most often responsible for these inflammatory responses more pronounced.

The role of RAS in the inflammatory process was further evidenced by the ability of an ACE inhibitor to suppress inflammation and subsequent tissue injury (Pupilli et al., 1999). Some studies suggest that losartan, an At1 blocker, and lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, can inhibit both the liver fibrosis and portal hypertension occurring in secondary biliary cirrhosis by inhibiting hepatic stellate cells (HSCs) activation (Agarwal et al.,1993). Other studies in vitro of cultured pancreatic stellate cells have demonstrated that these cells exhibit morphological and functional features similar to cultured hepatic stellate cells, including positive SMA staining after a period of time in culture, increased proliferation in response to PDGF, and increased collagen synthesis in response to TGF-β (Gressner et al., 1995). So these stellate cells could trigger an inflammatory process in the tissue which is expressed.

Although other tissues, these stellate cells can not express the AT1 and AT2 receptors are widely distributed throughout the system and this can lead to a local inflammatory response by angiotensin II signaling. Given this relationship, it is necessary to comment briefly on the mechanism of action of antihypertensive agents shown below.

ACE Inhibitors: The essential effect of the agents belonging to this group of drugs is just the inhibition of the conversion of angiotensin I to II. In this respect ACE inhibitors are selective

drugs, but because ACE has multiple substrates, these inhibitors may induce effects not related to reduced synthesis of angiotensin II. Among these various effects is the increased synthesis of bradykinin and prostaglandins that may contribute to the effects of ACE pharmacological inhibitors. A study by Silva, RB et al. (2010) in the Faculty of Medicine of Ribeirão Preto - FMRP / USP, Sao Paulo - Brazil, demonstrated that the application of drugs such as Lisinopril significantly reduced inflammatory response in an experimental model of acute pancreatitis, illustrating the relationship between the RAS and inflammation , figure 2.



A B

Fig. 2. Map showing histopathological in (A) - The severe inflammatory process in the experimental group of acute pancreatitis and (B) - A significant reduction in inflammation in animals treated with lisinopril (Silva, R et al, 2010).

Captopril: Captopril was the first ACE inhibitor to be marketed. This drug has a bioavailability of about 75% and undergoes rapid absorption. Most of this drug is excreted in the urine, about 40 to 50% in the form of captopril and the remainder in the form of dimers. Captopril contains a sulfhydryl group.

Enalapril: enalapril is a pro-drug hydrolyzed by esterases in the liver. After this hydrolysis, enalapril is converted into a dicarboxylic acid which is known as enalaprilat a highly potent inhibitor of ACE.

Lisinopril: This drug differently than enalapril, it is active. In vitro studies show that Lisinopril is an ACE inhibitor slightly more potent than enalaprilat. Our study showed that this drug also has significant anti-inflammatory effects, but these results we have shown this relationship only in a specific experimental model of acute pancreatitis, requiring a slightly larger study, to ascertain whether this behavior also occurs in human beings. Lisinopril does not accumulate in the tissues.

Fosinopril: This drug contains a phosphinate group that binds to the active site of ACE. Liver esterase is cleaved and, with this prodrug that is converted to fosinopril, more potent than captopril and less potent than enalaprilat.

In pathological conditions such as hypertension, ACE inhibitors promote the reduction of systemic vascular resistance and various hypertensive states. This effect, as mentioned above arises from the action of reducing the production of angiotensin II, thereby reducing their pressor effects and vascular remodeling. But what must be understood is that

angiotensin II has several other effects not only of increased blood pressure. These effects range from increased expression of proto-oncogene to the inflammation process. In the last decade studies have shown a strong relationship that RAS blockers possess anti atherosclerosis not only by regulating blood pressure, but also for its anti-inflammatory and antioxidant (Montecucco et al, 2009 and Schmieder et al, 2007). In this sense it is observed that studies that angiotensin II also acts on the expression of adhesion molecules such as intracellular adhesion molecule (ICAM), vasocelular adhesion molecule (VCAM), the P-selectin molecules expressed in the inflammatory process, and promote the expression of chemokines, growth factors and cytokines. Our study showed that angiotensin promotes the activation of certain stellate cells, which promote active since the deposition of collagen formation and fibrosis. So regardless of the mechanisms involved ACE inhibitors have broad clinical utility as antihypertensive agents, but also has a great potential for the therapy of other vascular disorders, and it is observed in experimental models.

Similarly antagonists of angiotensin II receptor act in lowering blood pressure, but unlike the effects of ACE inhibitors are not from inhibition of angiotensin II formation, but inhibition of its effects by antagonism of this peptide . This class of drugs bind to the AT1 receptor with high affinity and, in general, are around 10,000 times more selective for this receptor than for the AT2. The pharmacology of these antagonists is well described in the literature. Goldman and Gilman shows that studies in vitro and in vivo of these drugs block the majority of the biological effects of angiotensin II such as contraction of vascular smooth muscle, fast pressor responses, slow pressor responses, thirst, release of vasopressin, aldosterone secretion , release of catecholamines by the adrenal glands, increased noradrenergic neurotransmission, increased sympathetic tone, impaired renal function, cellular hypertrophy and hyperplasia, and inhibit the activation of pancreatic stellate cells, protecting from injuries such as acute pancreatitis, the latter effect was observed by Silva, RB. et al, 2010. Drugs that make up this group are: *candesartan, eprosartan, ibesartan, losartan, olmesartan, telmisartan and valsartan.*

Given this overview of the RAS and its relation to inflammation, we can observe that the drugs used to treat hypertension are consistent with the possible protective effects of a serial of inflammatory disorders. However the application of these to treat acute problems like apancreatite, for example, is not observed, but promising results from several studies, show that these drugs may be important in the treatment of various inflammatory disorders, is atherosclerosis, ischemia , or even pancreatitis. We observed in our work that pancreatic stellate cells respond to the action of angiotensin II (Figure 3 and 4) and in addition, we observed that these respond directly, because these cells have receptors for angiotensin II AT1 as illustrating the existence of even a Local RAS, regulating the vasculature of the tissue in question. Because of this, these drugs as mentioned above, could be a viable alternative to treat these other disorders.

In our study we observed that the strength pancreatic stellate cells in collagen production are involved during acute pancreatitis and possibly that these can become active cells through the action of angiotensin II produced by rennin-angiotensin system. However it has been suggested an increasingly close relationship between the RAS and the inflammatory process in this sense these studies indicate a relationship of therapy used to treat hypertension is also feasible in other disorders such as inflammatory problems.

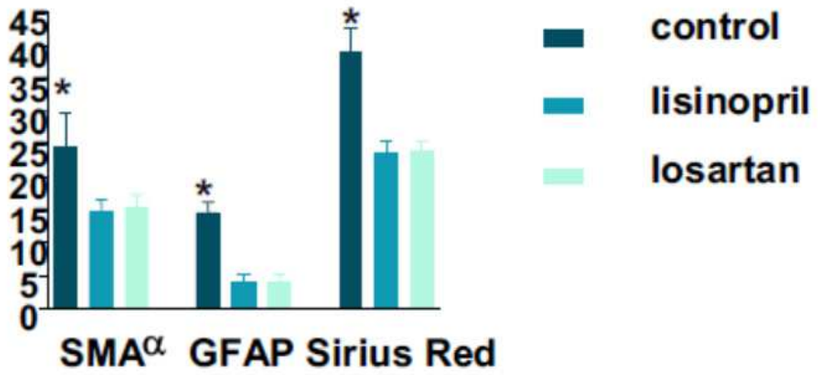


Fig. 3. Comparison of the number of pancreatic stellate cells marked for alpha-smooth muscle actin (α-SMA) and fibrillary acidic protein glial (GFAP), and the percentage of points scored by used. The (PS), between the pancreas of control rats treated with lisinopril and losartan. The bars represent the mean ± SD. * P <0.001, compared to the treaties.

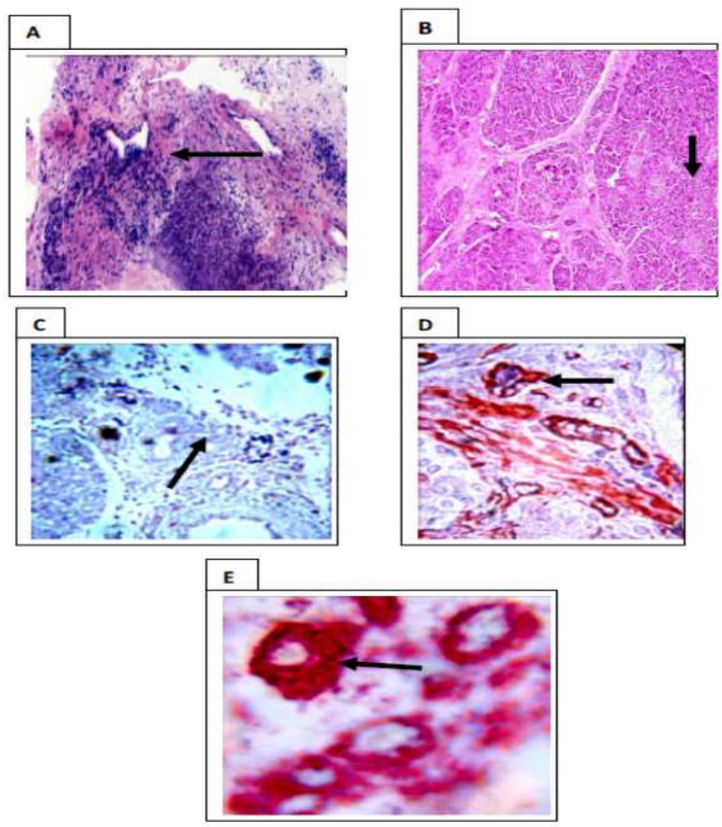


Fig. 4. Slides stained by hematoxylin and eosin (A) to inflammatory analysis have showed more neutrophylic inflammatory infiltrate in sample of control group measured in [purple]. Moreover slides stained by Sirius red (B) have showed more collagen deposit in the animals of control group too showed in [eosinofilic]. In the group treated (C) and stained by immunohistochemical staining method (GFAP or α-SMA) have less PSCs activated marked in [blue] compared with animals control (D and E) which have more PSCs activated measured in [red] ($p<0.05$)

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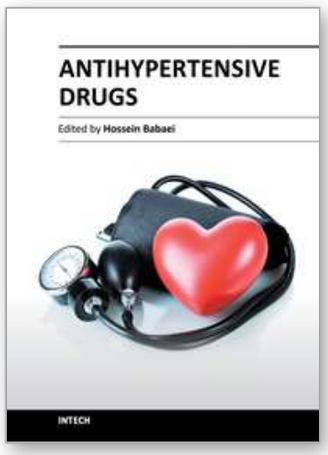

Antihypertensive Drugs

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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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