REVIEW ARTICLE

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Evaluation of the cardioprotective and antihypertensive effect of AVE 0991 in normotensive and hypertensive rats

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INTRODUCTION

Arterial pressure, or blood pressure (BP), consisting of the pressure that is generated by blood flow over the blood vessel wall, is determined by the volume that is ejected from the heart into the arteries during cardiac systole and arterial elastance and the rate in which blood flows out of the arteries. This generated pressure, in ideal values, guarantees the supply of oxygen and nutrients to the tissues[1]. BP control occurs through the synergistic interaction between various systems, through hemodynamic, neural, humoral, and renal processes[2]. Changes in these regulatory systems can lead to the development of systemic arterial hypertension (SAH)[3].

Systemic arterial hypertension (SAH) is one of the leading chronic diseases that affect individuals worldwide. When uncontrolled, it can dramatically increase the risk of complications such as stroke, coronary artery disease, and kidney and heart failure[4], in addition to representing the primary risk factor for death worldwide[5].

In the pathophysiology of SAH, several mechanisms may be related to its development and progression, such as oxidative stress, increased activity of matrix metalloproteinases[6], inflammation, expression and activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits[7], increased baroreflex sensitivity[8], and increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS)[3].

Renin-angiotensin-aldosterone system (RAAS) is one of the main components of fluid and electrolyte volume control and BP. The cascade of reactions leads to angiotensin II (Ang-II), an octapeptide that promotes vasoconstriction, stimulates the release of aldosterone, and promotes an increase in sodium and water reabsorption, generating an increase in BP[8,9]. Overactivation of this system, mainly through type I angiotensin receptors (AT1), can result in deleterious effects on the cardiovascular and renal systems[9].

Recent evidence has shown that in addition to the pathways related to the classical RAAS pathway, there are other components with opposite activities. These include angiotensin 1-9, alamandine, and angiotensin 1-7 [Ang-(1-7)], the latter being a product of the conversion of Ang-II by the converting enzyme-type II angiotensin (ACE-2) (Figure 1), related to an axis of beneficial activities and opposite to the classic RAAS pathway, and mediated by the action of its binding on MAS receptors[9,10]. MAS receptor agonists have been used in studies as a possible alternative for SAH treatment due to their vasodilatory activities, among them AVE 0991, a synthetic non-peptide agonist of this receptor, which showed cardiorenal protective effects in diabetic rats[11,12]. Hence, the objective of this study was to evaluate the effect of the agonist AVE 0991 on the cardiovascular system of hypertensive and normotensive rats, specifically if it promotes cardioprotective and antihypertensive effects and by what mechanisms these effects are generated.

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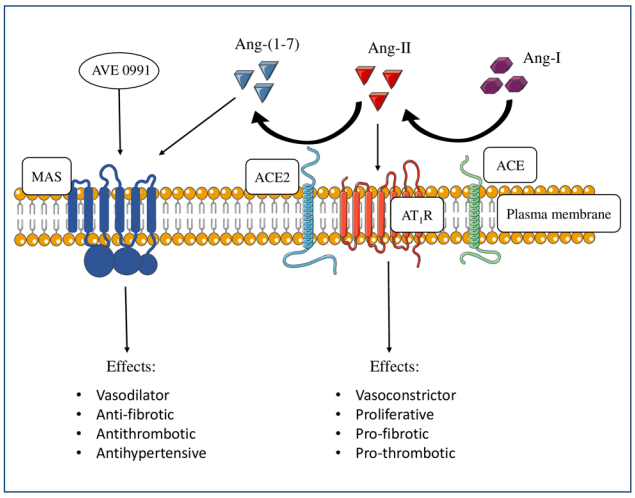

Figure 1. Actions generated by the ligation of AVE 0991 on the MAS receiver. Ang-II is converted to Ang-(1-7) by ACE2. Binding of Ang-(1-7) or other agonists, such as AVE 0991, on MAS receptors, generates effects contrary to those of binding of Ang-II on AT1 receptor.

METHODOLOGY

This is an integrative literature review study with a qualitative and descriptive character. The research brought together international studies to assess the effects of binding a non-peptide MAS receptor agonist and its effects on the cardiovascular system. The elaboration of this integrative review, as recommended, followed six steps[13]:

- Identification of the theme and selection of the guiding question
- Establishment of inclusion and exclusion criteria for studies
- Extraction of information to be extracted and categorization of selected studies
- Evaluation of included studies
- Interpretation of results
- Presentation of the review/synthesis of knowledge

Formulation of the review question

The following questions generated led to the review: Does the binding of the non-peptide agonist AVE 0991 to the MAS receptor promote cardioprotection and BP reduction in rats? And what are the actions related to the cardioprotective and antihypertensive effect of the interaction between AVE 0991 and the MAS receptor?

Literature search strategy

The bibliographic survey was developed through the electronic databases National Library of Medicine (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Elsevier Database (Scopus). The search terms used during the survey were as follows: "Hypertension," "Renin-Angiotensin System," "Angiotensin 1-7," and "AVE0991." The combination of terms was performed using the Boolean connector "AND."

Inclusion and exclusion criteria

The inclusion criteria were as follows: studies that addressed the effects generated by AVE 0991 on the cardiovascular system of hypertensive or normotensive rats; studies published in full, in English; and titles published in the period it comprises (2002–2022). Duplicate studies, clinical studies, and gray literature materials, such as theses, dissertations, course conclusion works, and studies published in event proceedings, were excluded.

Search and selection process

The literature search was performed in December 2021. To assist in identifying and selecting studies, the Statement for Reporting Systematic Reviews and Meta-Analyses of Studies (PRISMA) flowchart was used (Figure 1).

Data extraction and analysis

From the selection of the studies, a thorough analysis of the studies was carried out. The studies were characterized in author/year of publication, title, experimental model, and cardioprotective and antihypertensive actions generated by the treatment with AVE 0991 through a standardized data form as shown in Figure 2.

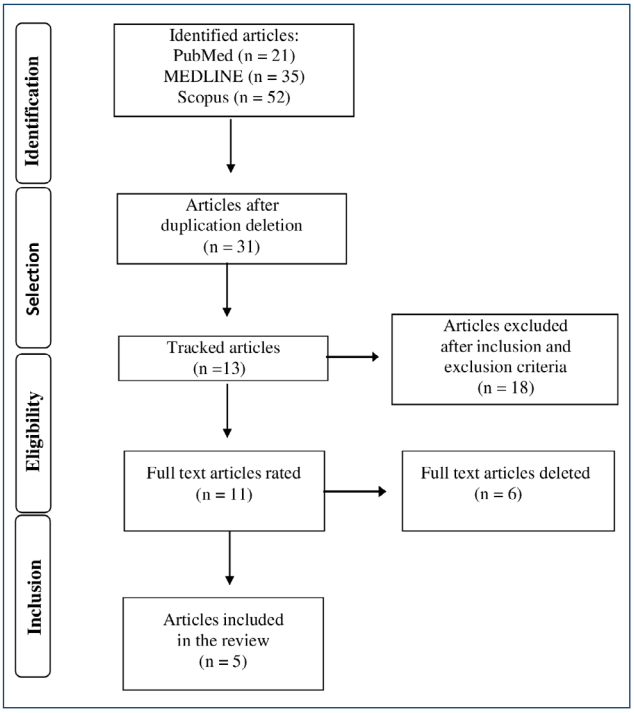

Figure 2. Flowchart of the article selection process.

RESULTS

The titles identified by searching the PubMed, MEDLINE, and Scopus databases corresponded to 108 articles. After excluding duplicates, 31 articles returned, of which, after reading the texts and abstracts applying the inclusion criteria, 5 articles remained for reading the entire text in full, as shown in Figure 1.

The results of this integrative review summarize the cardioprotective and antihypertensive effects generated by treatment with a non-peptide agonist of the MAS receptor, i.e., AVE 0991, in rats with and without hypertension. The summary of the studies included in this review is shown in Table 1, which is characterized and described according to the author, year of publication, article title, experimental model, and cardioprotective and antihypertensive actions induced by AVE 0991.

This brief review had numerous limitations. A limited number of studies were identified that addressed the use of AVE 0991 and its effects on the cardiovascular system. Given the limited number of studies found, the time interval used was 20 years to enhance the search for studies and provide as much evidence as possible. However, the results obtained were enough to show that using AVE 0991 plays beneficial actions on the cardiovascular system, such as those already described related to Ang-(1-7).

DISCUSSION

The RAAS cascade consists of converting angiotensinogen into Ang-I by an enzyme released by the juxtaglomerular cells of the kidney, renin. Ang-I, in turn, is enzymatically converted by the ACE into Ang-II. When Ang-II binds to the AT1 receptor, it promotes various activities, including vasoconstrictor, proliferative, pro-inflammatory, pro-fibrotic, and pro-thrombotic effects[8,14]. On the other hand, Ang-II can be converted to Ang-(1-7) through ACE-2. Through its binding to MAS receptors, Ang-(1-7) promotes effects contrary to Ang-II, such as vasodilator, anti-thrombotic, antihypertensive, and anti-fibrotic (Figure 2)[14].

Although Ang-(1-7) supplementation seems promising for the treatment of cardiovascular diseases, including SAH, by reducing the contractile response of Ang-II and in the long term attenuating vascular remodeling and BP[15], there are limitations; the peptide has a short biological half-life and is not helpful for oral ingestion[16]. With a longer half-life and stability, these peptide analogs, such as AVE 0991, have drawn research attention[11]. AVE 0991 is a selective non-peptide agonist of the MAS receptor. MAS is a G-protein-coupled receptor discovered in the 1980s, but its binding relationship with Ang-(1-7) was only discovered in the 2000s[17]. The MAS receptor, Ang-(1-7), and ACE-2 form the so-called ACE2-Ang-(1-7)-Mas

Table 1. Distribution of articles included in the review, according to author, year, experimental model, and AVE 0991 action.

Author/year	Title	Experimental model	Cardioprotective and antihypertensive action induced by AVE 0991
Cunha et al., 2013[12]	The non-peptide Ang-(1-7) mimic AVE 0991 attenuates cardiac remodeling and improves baroreflex sensitivity in renovascular hypertensive rats	Fischer rats with renovascular hypertension 2 kidneys 1 clip	Treatment with AVE 0991 reduced fibrosis, inflammation, and increased cardiac weight, in addition to improving baroreflex sensitivity and blood pressure.
Ferreira et al., 2007[21]	Isoproterenol-induced impairment of heart function and remodeling are attenuated by the non-peptide Ang-(1-7) analog AVE 0991	Normotensive Wistar rats treated with isoproterenol	Treatment with AVE 0991 in rats undergoing chronic isoproterenol treatment prevented muscle hypertrophy and collagen fiber deposition in the heart, in addition to improving cardiac function.
Raffai and Lombard, 2016[23]	Ang-(1-7) selectively induces relaxation and modulates endothelium-dependent dilation in mesenteric arteries of salt-fed rats	Sprague-Dawley rats fed a high-salt diet	Oral treatment with AVE 0991 promotes vascular relaxation and improves relaxation of other vasodilators such as bradykinin and acetylcholine and promotes vasoprotective effect.
Zeng et al., 2010[22]	Impairment of cardiac function and remodeling induced by myocardial Infarction in rats are attenuated by the non-peptide Ang-(1-7) analog AVE 0991	Normotensive Sprague-Dawley rats with coronary artery ligation	Treatment with AVE 0991 was able to attenuate hypertrophy and increase in cardiac weight, in addition to improving cardiac function after myocardial infarction.
Carvalho et al., 2007[24]	Evidence for MAS-mediated bradykinin potentiation by the Ang-(1-7) non-peptide mimic AVE 0991 in normotensive rats	Normotensive Wistar rats	Treatment with AVE 0991 improved the action of bradykinin through a mechanism related to the activity mediated by the MAS receptor and potentiated the release of nitric oxide.

axis, with actions supporting and regulating the traditional ACE-Ang II-AT1 axis[18,19].

A study carried out in hypertensive animals with two kidneys one clip treated for 28 days with AVE 0991 showed that the treatment was able to reduce collagen deposition and thickening of the heart induced by hypertension and reduce cardiac and renal inflammation, thus improving baroreflex sensitivity and BP[12]. This is in agreement with a study carried out in China, where treatment with AVE 0991 for 4 weeks was able to attenuate the thickening and hypertrophy of cardiomyocytes induced by pressure overload, in addition to improving cardiac function, evidenced by the increase in ejection fraction and increase in the ventricular shortening fraction[20].

Ferreira et al. evaluated the treatment with AVE 0991 on the remodeling of the heart in a model of cardiac dysfunction induced by treatment with isoproterenol, a non-selective agonist of beta-adrenergic receptors. Treatment with AVE 0991 reduced myocardial hypertrophy and the deposition of collagen fibers in the heart, in addition to improving cardiac function[21]. Similarly, in a study carried out with an experimental model of myocardial infarction, it was observed that treatment with AVE 0991 generated anti-hypertrophic and anti-fibrotic actions on the heart, preserving systolic function and reducing the synthesis and deposition of collagen type I and type III in the heart[22].

A previous study showed that oral treatment with the non-peptide agonist AVE 0991 in Sprague-Dawley rats fed with a high-sodium diet effectively improved vascular function and promoted vasodilatory and vasoprotective effects[23]. In addition, treatment with AVE 0991 improved the action of an endogenous vasodilator, bradykinin[24]. This shows that AVE 0991 has beneficial actions similar to Ang-(1-7) in the cardiovascular system, including reduced cell proliferation, inflammation, oxidative stress, vascular remodeling, and fibrosis[25].

CONCLUSION

The results showed that the use of AVE 0991 generates cardioprotective actions in hypertensive and normotensive rats, in addition to promising antihypertensive activity. AVE 0991 reduced inflammation, cardiac remodeling and fibrosis, and oxidative stress. In addition to improving baroreflex sensitivity, it reduces BP and vascular changes resulting from SAH.

AUTHORS' CONTRIBUTIONS

MVBS: Conceptualization, Writing, Formal Analysis, Methodology. **CPSJ**: Data curation. **FIMF**: Data curation. **AOB**: Supervision. **HVCS**: Visualization, Supervision, Edition. **VMS**: Visualization, Supervision, Edition. **JACRTM**: Visualization, Supervision, Edition.

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