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The compensatory renin-angiotensin system in the central regulation of arterial pressure: New avenues and new challenges

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Abstract

Hypertension is a widespread condition that affects millions of people around the world and has a great impact in public health. The classic Renin Angiotensin System is a complex system comprised of multiple peptides and pathways that have been the motive of great drug development over the years to control hypertension. However, there are still patients whose hypertension is very difficult to control with the current drugs and strategies, thus motivating further research in this field. In the last two decades, important discoveries have expanded our knowledge of this system and new pathways are emerging that are helping us understand the complex interaction taking place not only in the periphery but also in the central nervous system where the renin angiotensin system is also very active. A new arm, called the ACE2/Ang-(1-7)/Mas receptor axis was shown to exert anti-hypertensive properties and serve as a counterbalance to the classic ACE/Angiotensin-II/AT1 receptor axis; in this way, modulating or even counteracting the negative effects of Angiotensin-II in blood pressure regulation and water retention. Modulation of this new axis through ACE2 activation, ADAM17 regulation or AT1 receptor internalization are some of the novel avenues and challenges that have the potential to become target for new drug research and development for the treatment of hypertension.

Keywords

ADAM17; oxidative stress; DOCA-salt hypertension; antioxidant; ACE2; Angiotensin II

Hypertension is classically defined in adults as systolic blood pressure (BP) higher than 140 mmHg and/or diastolic BP higher than 90 mmHg. Pre-hypertension is defined as systolic BP >120 mmHg and diastolic BP > 80 mmHg, but not reaching hypertension levels according to the Joint National Committee (JNC) 8 for hypertension guidelines [James *et al.*, 2014]. Thresholds for pediatric patients vary according to age.

Hypertension is a multifactorial disease, the etiology of which is not completely understood [Yemane *et al.*, 2010]. It has reached epidemic proportions worldwide and contributes significantly to the burden of heart disease, stroke, kidney failure, disability and premature death [Neupane *et al.*, 2014]. It is estimated that about 17 million deaths occur worldwide

because of cardiovascular diseases every year, of which, complications of hypertension alone account for 9.4 million deaths [2011]. A third of US adults are reported to be pre-hypertensive [Yoon *et al.*, 2015]. Prevention is an important step in the pre-hypertensive group to reduce the number of people affected by high BP and consequently the number of deaths due to cardiovascular complications arising from hypertension. Emphasis is placed on those with pre-hypertension in order to prevent the development of high BP by adopting a healthier lifestyle like increasing exercise activity, reducing salt consumption and reducing smoking, among others. However in spite of the effort and self-care, there is still a great population of patients who will eventually require pharmacological treatment.

Current strategies to manage hypertension

According to the recent Joint National Committee (JNC) 8 meeting, the current recommendations for treatment of hypertension are mainly based on the use, alone or in combination, of 4 classes of medications which include: diuretics, calcium channel blockers, angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEI). All of these medications have proved to be adequate to decrease BP enough to be maintained below the threshold levels for the age population [James *et al.*, 2014]. There is however a >30% of patients whose hypertension cannot be controlled [Yoon *et al.*, 2015] with the current recommendations and require novel interventions or additional drugs to their treatment regimen with variable rate of success [Persell, 2011]. Therefore, the question of finding new treatment strategies is still a major concern in pharmacological research.

The Renin Angiotensin System

The classic renin angiotensin system (RAS) is a complex system composed of numerous peptides, enzymes and receptors that are involved in BP regulation and fluid homeostasis. It starts with angiotensinogen (AGT) generated in the liver. AGT is converted to angiotensin (Ang)-I by renin that is released from juxtaglomerular cells of the kidney under salt deprivation and fluid imbalance. Ang-I acts as a substrate for angiotensin converting enzyme (ACE) which cleaves it to form Ang-II (Fig 1). Ang-II signaling via G protein-coupled AT1 receptors (AT1R) promotes vasoconstriction, increases sympathetic tone, vasopressin release and aldosterone secretion. All of these effects ultimately increase the effective fluid volume and elevate BP. To a lesser extent Ang-II also signals through a second G protein-coupled receptor, namely AT2 (AT2R), promoting vasodilatory effects opposite to AT1R through the release of NO.

Although the RAS is classically thought to act as an endocrine system with Ang-II circulating throughout the bloodstream, components have been shown to exist locally in several tissues including the heart, lung, adrenal gland, kidney, blood vessels and brain, to name only a few [Lavoie *et al.*, 2003, Paul *et al.*, 2006].

The brain RAS produces Ang peptides locally in several regions involved in the central regulation of BP, such as the paraventricular nucleus of the hypothalamus (PVN), subfornical organ (SFO), rostral ventrolateral medulla (RVLM), area postrema, and nucleus tractus solitarius (NTS) [Davisson, 2003, Gironacci *et al.*, 2014]. Increased circulating Ang-II acts by controlling sodium and water intake by acting on structures of the antero-ventral

region of the third ventricle (AV3V), stimulating the secretion of vasopressin from the PVN and supraoptic nuclei of the hypothalamus, and controlling autonomic function by increasing sympathetic nerve activity in several nuclei including the PVN and RVLM [Ferguson *et al.*, 1997].

Over-activity of the brain RAS has been implicated in neurogenic hypertension and is associated with excessive levels of Ang-II [Grobe *et al.*, 2010]. In addition, to the circumventricular organs (CVO), which are brain regions lacking a blood-brain barrier and allowing small, circulating peptides like Ang-II to cross [Johnson *et al.*, 1993], evidence suggest that the blood brain barrier becomes “leaky” during the development of hypertension [Ueno *et al.*, 2004] thus allowing more Ang-II to enter the central nervous system .

Therefore, not only locally-generated Ang-II interacting with RAS components within the blood-brain barrier (PVN and RVLM), but also circulating Ang-II can enter the brain and interact with Ang receptors, notably AT1R, to produce sympathetic activation in addition to peripheral effects and further exacerbate the over-activity of the brain RAS in neurogenic hypertension [Lazartigues *et al.*, 2007, Xia *et al.*, 2009].

Targeting the RAS

Strategies to treat hypertension and heart failure have focused on blockade (Fig 2) of Ang-II formation (i.e. ACEI and more recently renin inhibitors) and blockade of the AT1R (i.e. Angiotensin receptor blockers). Blockade of the RAS with these drugs is beneficial but not absolute and results in arterial and venous vasodilation, natriuresis and diuresis, decrease in sympathetic nervous activity, and inhibition of cardiac and vascular hypertrophy. These effects lead to a reduction in BP and less vascular remodeling in the pathology of hypertension [Brunner *et al.*, 1979]. Accordingly, RAS inhibitors are also effective anti-hypertensive treatments in patients with low plasma renin levels, a phenomenon seen in neurogenic hypertension [Sigmund, 2010] and correlate with 25% of those diagnosed with low renin hypertension [2011]. Renin inhibitors, such as Aliskiren, target the conversion of AGT to Ang-I and thus reduce the substrate available for metabolism into Ang-II. Another peptide in the RAS, Ang-(1-12), can be cleaved by ACE and converted into Ang-I, followed by a second cleavage by ACE into Ang-II, thus bypassing the effects of renin [Westwood *et al.*, 2012] and suggesting that renin inhibitors may not completely block the formation of Ang-II. Nagata *et al.* reported that administration of Ang-(1-12) in the periphery increases BP. This pressor response was attenuated by the AT1R blocker candesartan and the ACEI captopril [Nagata *et al.*, 2006] suggesting that Ang-II stimulation of AT1R remains the main pressor mechanism.

ACEI like captopril, lisinopril and enalapril, block the cleavage of Ang-I to Ang-II and lead to an overall decrease in circulating Ang-II levels. However, chymase has been shown to catalyze the formation of Ang-II from Ang-I [Park *et al.*, 2013] independently of ACE. This was particularly evident in the face of diabetic and hypertensive nephropathy which allows Ang-II to bypass the effects of ACEI to some extent. ACEI also inhibit the catabolism of bradykinin [Tom *et al.*, 2001], a molecule that produces vasodilatory effects via its B2

receptor and mediates inflammation through its B1 receptor. This dual action of ACEI provides great therapeutic benefits in treating cardiovascular diseases.

A final set of inhibitors targeting the RAS, blocks the AT1R, through which Ang-II promotes the majority of its signaling effects [Allen *et al.*, 2000]. These drugs are commonly referred to as sartans or ARB. While only minor effects of Ang-II are attributed to the AT2R in normal conditions, the role of this receptor appears to be more prominent in pathological conditions (e.g. hypertension), as evidenced by recent data [Xu *et al.*, 2011, Bruce *et al.*, 2014, Sampson *et al.*, 2015]. Blocking AT1R increases circulating Ang-II levels, leading to increased signaling through AT2R (and ACE2). Like ACEI, ARB also provide beneficial effects in the treatment of hypertension by decreasing Ang-II signaling via the AT1R.

The ACE2/ANG-(1-7)/Mas Axis

In the past decade, a new axis of the RAS, Angiotensin Converting Enzyme Type 2 (ACE2)/Ang-(1-7)/Mas receptor, has been identified (Fig. 3) and shown to exhibit compensatory mechanisms in the face of an overactive RAS [Xu *et al.*, 2011]. The components of this new axis have been identified in regions of the brain involved in the central regulation of BP, as well as the periphery, and are thought to play a role in neurogenic hypertension [Lazartigues *et al.*, 2007]. ACE2 is a homologue of ACE that cleaves Ang-II into the vasodilator peptide Ang-(1-7), which acts on the Mas receptor to produce effects opposite to Ang-II, such as vasodilatation, anti-proliferation and anti-hypertrophy [Ferrario *et al.*, 2005]. ACE2 (and AT2R) may also be providing some of the beneficial effects seen with ARB, which increase Ang-II levels, by allowing for ACE2 to cleave more Ang-II substrate into Ang-(1-7). ACE2 can also cleave Ang-I into Ang-(1-9), which could then be converted into Ang-(1-7) by ACE or neprilysin [Vickers *et al.*, 2002]. However, the affinity for this reaction is much less than for Ang-II and it appears that this path would only be activated when Ang-I levels are elevated, for example in the presence of ACEI due to blocking the conversion of Ang-I into Ang-II, leaving Ang-I available for cleavage by ACE2 (Fig 3).

Several studies have highlighted ACE2 as a pivotal player in counterbalancing the vasoconstrictive actions of Ang-II in the development of cardiovascular diseases. The development of Ang-II-induced hypertension was blunted by overexpression of ACE2 in the central nervous system [Feng *et al.*, 2010]. In similar studies, rodents were also protected from impaired baroreflex and autonomic dysfunction induced by Ang-II when ACE2 was overexpressed in the brain [Yamazato *et al.*, 2007, Xia *et al.*, 2009]. Other studies have reported that ACE2 prevents cardiac hypertrophy in Ang-II infused animals [Crackower *et al.*, 2002, Diez-Freire *et al.*, 2006] [Feng *et al.*, 2012]. Finally, high BP is decreased by ACE2 overexpression from lentivirus introduced to the RVLM of spontaneously hypertensive rats [Yamazato *et al.*, 2007]. In these studies, ACE2 not only reduces the levels of Ang-II but also increases the levels of Ang-(1-7), promoting beneficial effects in various cardiovascular diseases. Therefore, therapies to enhance ACE2 could become a new approach for the treatment of cardiovascular diseases.

Potential new targets and new challenges

Although not part of the compensatory RAS *per se*, the previously identified (Pro)-renin receptor (PRR) [Nguyen *et al.*, 2008] has recently been shown to play a critical role in the central regulation of BP. Not only the PRR was shown to be expressed in key brain nuclei involved in the regulation of autonomic function but it is also up-regulated with hypertension [Li *et al.*, 2012, Zubcevic *et al.*, 2013, Li *et al.*, 2014]. Interestingly, one of these groups recently reported the generation of a new PRR antagonist, termed PRO20, capable of dose-dependently inhibiting PRR-induced hypertension in mice [Li *et al.*, 2015]. Prevention of increased Ang-II levels within the central nervous system was shown to contribute to the anti-hypertensive effects of PRO20 which could potentially be the first of a new class of anti-hypertensive agents.

At the other end of the RAS cascade, Ala¹-Ang-(1-7), aka Alamandine, was identified as a new metabolite of Ang-(1-7) through an unidentified enzyme [Lautner *et al.*, 2013]. Alamandine can also be formed, via ACE2, from Ang-A, an analogue of Ang-II identified in human plasma [Jankowski *et al.*, 2007, Etelvino *et al.*, 2014]. So far, reports show that Alamandine has similar properties to Ang-(1-7), capable of promoting nitric oxide signaling, reducing Ang-A-mediated vasoconstriction and with anti-hypertensive properties. Alamandine was reported to bind the MrgD receptor which can also be activated, *in vitro*, by β -alanine, GABA, BABA and Ang-(1-7) [Solinski *et al.*, 2014]. However recent studies have suggested that heterodimerization of receptors, including the AT2R, could mediate the effects of Alamandine and Ang-(1-7) [Villela *et al.*, 2015]. More work is needed to determine the specificity of Alamandine for these receptors *in vivo*. Of particular interest, a new endopeptidase was recently identified in the brain and kidney, capable of hydrolyzing Ang-(1-7) and Alamandine [Wilson *et al.*, 2015]. Once identified, this new endopeptidase might be of importance as its inhibition would theoretically prolong Ang-(1-7) and Alamandine half-life and therefore their anti-hypertensive properties.

Besides the promising targets described above, researchers are also facing new challenges with the previously identified target: ACE2. Our laboratory recently identified 2 new post-translational mechanisms that may impair the ongoing efforts to elevate ACE2 activity and reinforce the enzyme's compensatory activity.

ADAM17 (A Disintegrin and Metalloproteinase 17) is a type I transmembrane protein that belongs to a superfamily of Zn-dependent metalloproteases. ADAM17 plays a key role in the regulation of the proteolytic release from cellular membranes of some cytokines, chemokines, growth factors and their receptors [Dreymueller *et al.*, 2012]. Increased ADAM17-mediated shedding has been described in a variety of diseases such as ischemia, heart failure, arthritis, atherosclerosis, diabetes, cancer, neurological and immune diseases. Recently, we demonstrated enhanced ADAM17 expression through a RAS over-activity-mediated mechanism leading to ACE2 down-regulation from the plasma membrane through shedding of its catalytic site, in the brain of DOCA-salt hypertensive mice [Xia *et al.*, 2013]. At the same time, treatment of neurons with Ang-II was shown to up-regulate the expression of ADAM17. Furthermore, knockdown of ADAM17 in the central nervous system using chronic infusion of small interference RNA blunted the development of hypertension in

these mice. This may suggest a deleterious effect of ADAM17 activity on ACE2 compensatory effects and potentially a new target for the treatment of neurogenic hypertension.

Another mechanism of ACE2 down-regulation has been proposed by our group, by suggesting that the hypertensive effects of ANG-II are in part mediated by internalization of membrane bound ACE2 and subsequent lysosomal degradation of this carboxypeptidase through an AT1R-dependent mechanism [Deshotels *et al.*, 2014]. Interestingly, a similar mechanism of AT1R-mediated internalization was very recently highlighted for another enzyme, Cox2 [Sood *et al.*, 2014]. This feed-forward mechanism, supporting the reduction of ACE2 would limit the formation and therefore availability of ANG-(1-7), as well as Alamandine, and enhance the hypertensive actions of ANG-II.

These studies emphasize the need for a better understanding of the mechanisms limiting ACE2 compensatory effects before the introduction of new therapies to enhance ACE2 activity.

Conclusion

Certainly, a great advance has been made in understanding the role of the renin-angiotensin system and ACE2 in the brain. The potential therapeutic implications of ACE2 and downstream peptides like Ang-(1-7) and Alamandine, make for ideal target candidates for further research in hypertension, heart failure, and other cardiovascular diseases. Increasing brain ACE2 by stimulating endogenous ACE2 activity and/or expression, or administration of exogenous ACE2 may provide beneficial effects in some pathologic conditions, mostly by reducing sympathetic activity, oxidative stress and inflammation which are the main mechanisms activated by the ACE/Ang-II/AT1R axis. Although the discovery of ACE2 and Alamandine have been recent advancements in our understanding of the compensatory RAS, further clarification of its role and therapeutic potential in the central nervous system in health and disease is needed.

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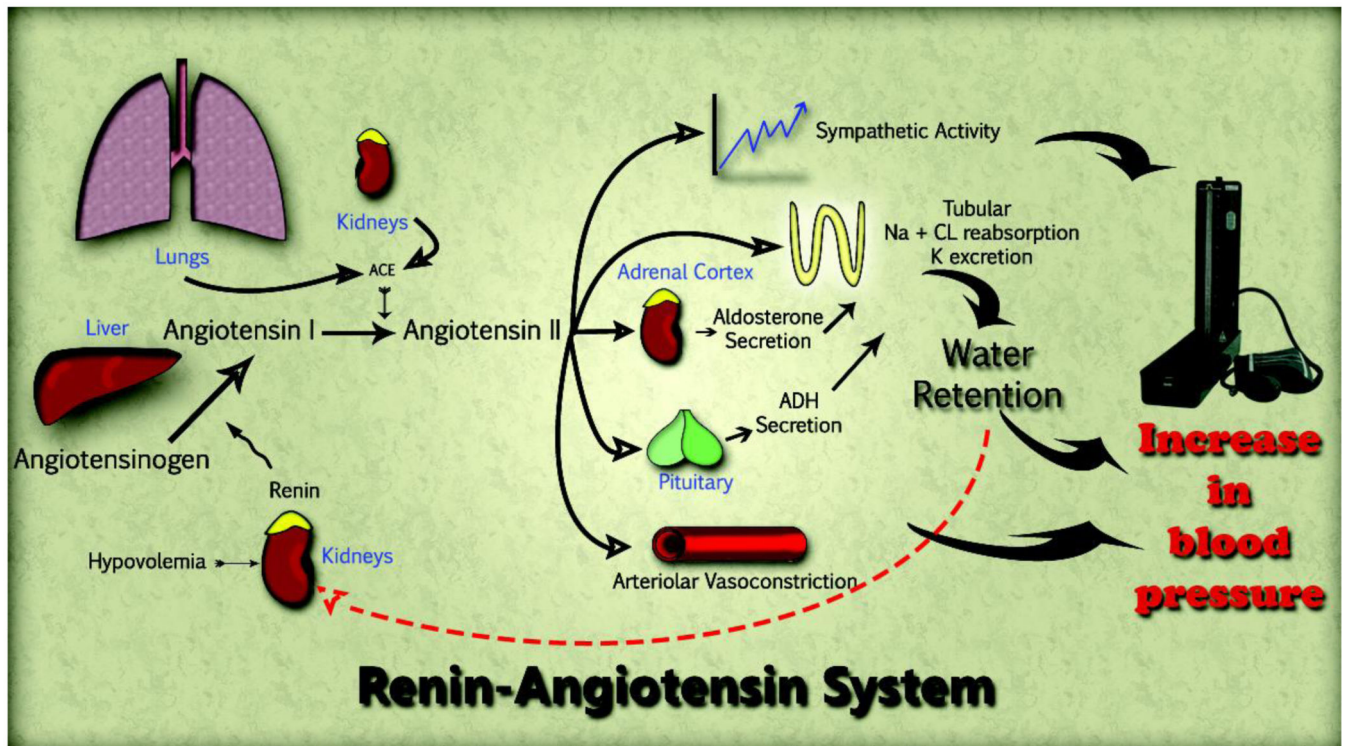


Figure 1.

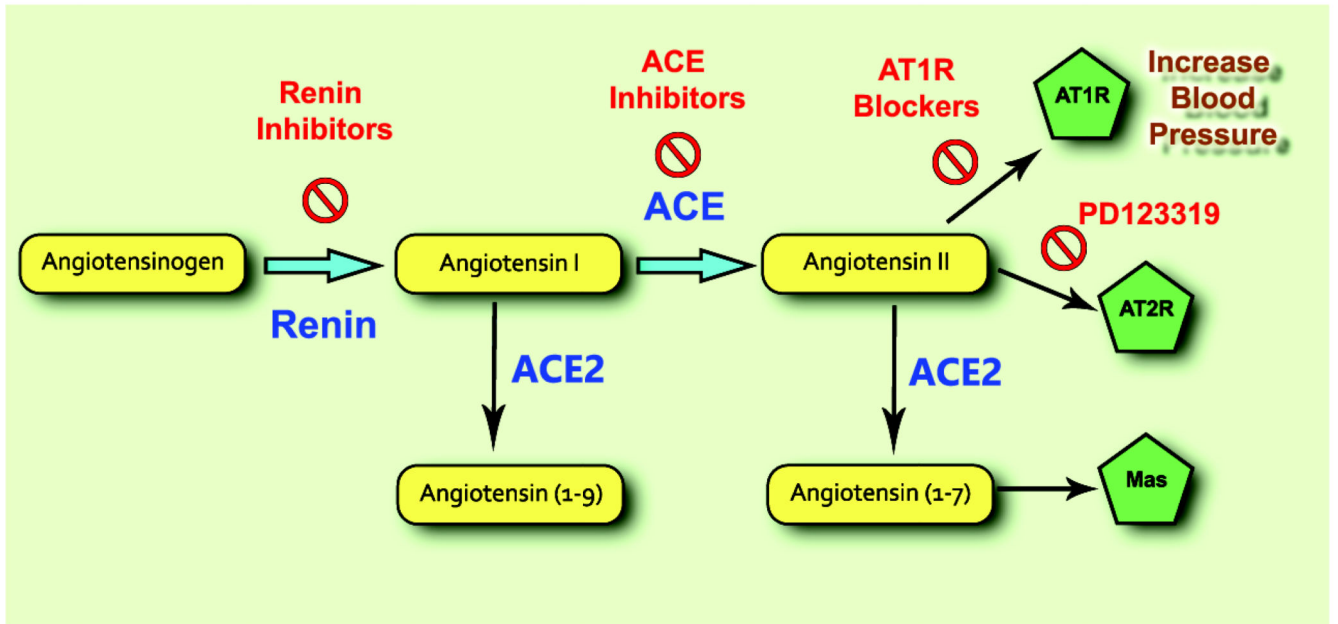


Figure 2.

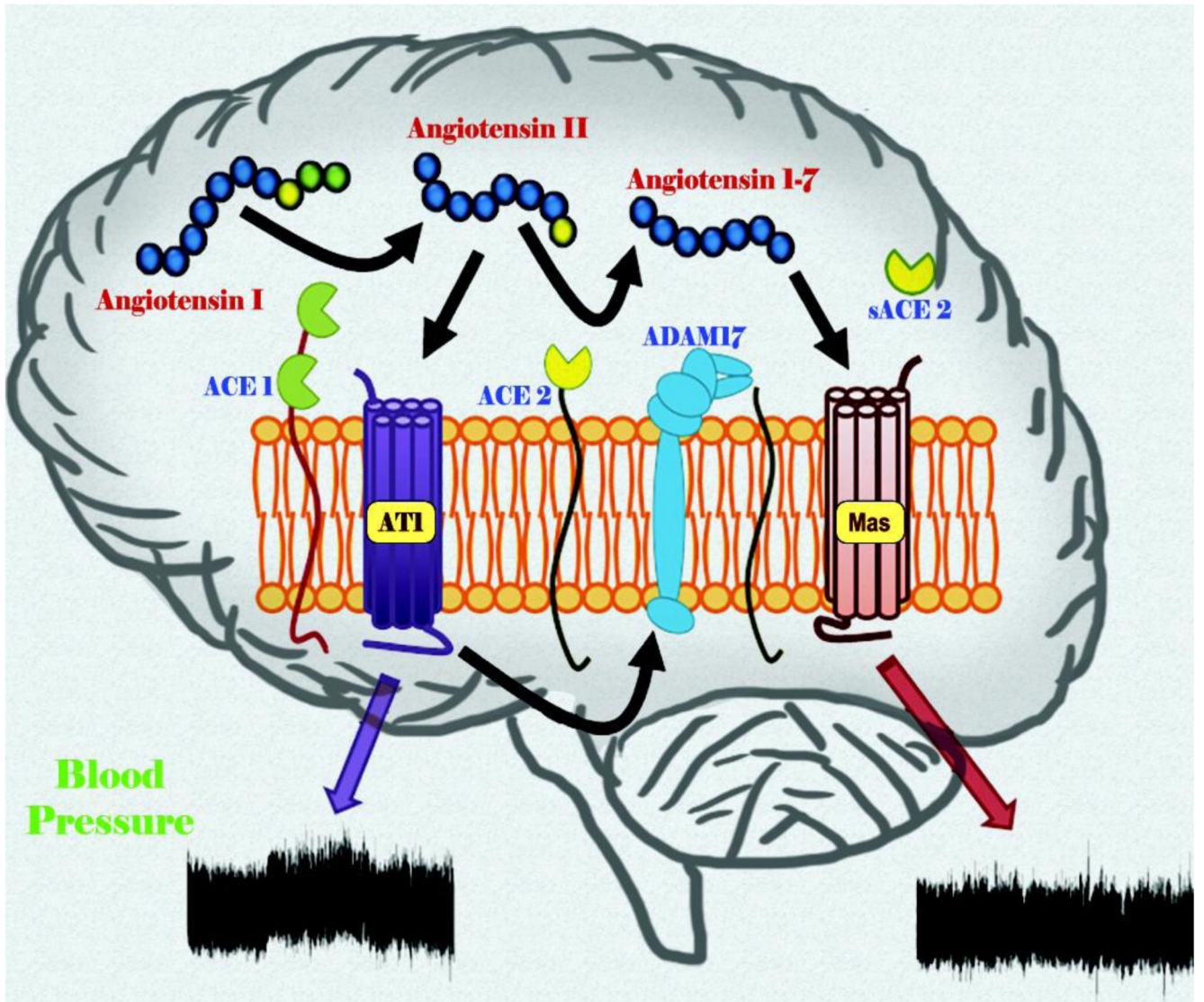


Figure 3.