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Gabriela Maria Lucera

Mechanistic insights into the effects of angiotensin II and sodium Intake on brain and kidney dysfunction in renovascular hypertension

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Mechanistic insights into the effects of angiotensin II and sodium Intake on brain and kidney dysfunction in renovascular hypertensionn

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Advisor: Débora Simões de Almeida Colombari

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Mechanistic insights into the effects of angiotensin II and sodium Intake on brain and kidney dysfunction in renovascular hypertension

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ABSTRACT

Renovascular hypertension (RVH) is a secondary form of hypertension characterized by excessive activation of the renin–angiotensin–aldosterone system (RAAS), increased sympathetic activity, and progressive brain and kidney injury. This thesis investigated how high sodium intake influences cardiovascular, intracranial, neuroinflammatory, and renal changes in the 2-kidney, 1-clip (2K1C) rat model and how these effects are modulated by AT_1 receptor blockade with losartan. In Manuscript 1, acute intravenous losartan (10 mg/kg) normalized mean arterial pressure (MAP) and intracranial pressure (ICP) in 2K1C rats drinking water, but not in those with access to hypertonic saline (0.3 M NaCl). Despite unchanged MAP and ICP, losartan improved intracranial cerebral compliance (ICC), suggesting enhanced brain compliance independent of pressure reduction. In Manuscript 2, 2K1C rats exhibited marked microgliosis and astrogliosis in the nucleus of the solitary tract (NTS), along with glomerular atrophy and collagen deposition in the clipped kidney. Short-term losartan normalized glial density and glomerular morphology but failed to reverse established renal fibrosis. In the area postrema, inflammation persisted despite AT_1 receptor blockade, suggesting the presence of Ang II-independent mechanisms. High sodium intake enhanced microglial proliferation but did not aggravate renal damage. Together, these findings demonstrate that Ang II–driven neuroinflammation and renal remodeling are central to RVH pathophysiology. Although losartan exerts neuroprotective and renoprotective actions, elevated sodium intake alters central mechanisms and limits the antihypertensive efficacy of AT_1 receptor blockade**.**

Keywords: Hypertension renovascular; Neuroinflammatory diseases; Intracranial hypertension;

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RESUMO

A hipertensão renovascular (HRV) é uma forma secundária de hipertensão caracterizada pela ativação excessiva do sistema renina–angiotensina–aldosterona (SRAA), aumento da atividade simpática e lesões progressivas no cérebro e nos rins. Esta tese investigou como a ingestão elevada de sódio influencia alterações cardiovasculares, intracranianas, neuroinflamatórias e renais no modelo experimental 2-rins-1-clipe (2R1C) e como esses efeitos são modulados pelo bloqueio do receptor AT_1 com losartana. No Manuscrito 1, a administração intravenosa aguda de losartana (10 mg/kg) normalizou a pressão arterial média (PAM) e a pressão intracraniana (PIC) em ratos 2R1C que ingeriam apenas água, mas não em aqueles com acesso à solução hipertônica de cloreto de sódio (0,3 M NaCl). Apesar de a PAM e a PIC permanecerem inalteradas, a losartana melhorou a complacência cerebral intracraniana (CCI), indicando aumento da complacência cerebral, independentemente da redução pressórica. No Manuscrito 2, ratos 2R1C apresentaram microgliose e astrogliose intensas no núcleo do trato solitário (NTS), além de atrofia glomerular e deposição de colágeno no rim clipado. O tratamento curto com losartana normalizou a densidade glial e a morfologia glomerular, mas não reverteu a fibrose renal. Na área postrema, a inflamação persistiu, sugerindo mecanismos independentes da ação da angiotensina II. Em conjunto, os achados indicam que a neuroinflamação e o remodelamento renal mediados pela angiotensina II são centrais para a HRV. Embora a losartana exerça efeitos neuro- e renoprotetores, a ingestão excessiva de sódio altera mecanismos centrais e reduz a eficácia do bloqueio do receptor AT_1.

Palavras-chave: Hipertensão vascular; Doenças neuroinflamatórias; Hipertensão intracraniana;

SUMMARY

1 INTRODUCTION

Cardiovascular diseases remain one of the leading causes of mortality worldwide. Among them, ischemic heart disease stands as the primary cause of death, followed by ischemic stroke[1]. Major risk factors for these conditions include elevated blood pressure and excessive salt intake, both of which are modifiable and therefore represent important targets for prevention and public-health interventions. Nonetheless, managing hypertension has become increasingly complex. The use of combination therapy is becoming more frequent and is often ineffective, both in primary and secondary hypertension[2]. The combination of reduced salt intake and medication has been effective in lowering blood pressure[3].

One relevant subtype of secondary hypertension, often characterized by resistance to pharmacological treatment, is renovascular hypertension[1,2]. In this condition, therapy typically focuses on pharmacological blockade of components of the renin–angiotensin–aldosterone system (RAAS)[3-5] while more invasive strategies, such as renal denervation, may be considered in refractory cases. Notably, approximately 25% of patients with renal artery stenosis (RAS) also exhibit resistant hypertension. One effect of angiotensin II (ANG II) in this type of hypertension is to increase salt intake[4]. High sodium intake has several deleterious effects on the body, including increased blood pressure[5].

We previously demonstrated that, in a 2-kidney-1-clip (2K1C), animal model used to mimic hypertension, animals that ingest hypertonic salt (0.3 M NaCl) show resistance to acute losartan treatment, an AT1 receptor blocker widely used by the population[6]. Accordingly, this study sought to elucidate how dietary salt intake modulates responses to losartan treatment in the 2K1C model, particularly with respect to intracranial pressure, cerebral compliance, neuroinflammatory responses, and renal injury. The following sections review the literature on these topics.

1.1 Salt Consumption and Hypertension

Consuming sodium in amounts that exceed the body's physiological requirements is a significant risk factor for cardiovascular disease, particularly hypertension, because it directly raises blood pressure[5,7-9]. It is important to emphasize that, while sodium is a critical nutrient and the primary cation in extracellular fluid (ECF), it must

be consumed in appropriate amounts to maintain effective homeostasis[10,11]. The body constantly exchanges ions and water, experiencing both gains and losses[12]. These losses can result from exposure to extreme heat, intense physical activity, or certain medical conditions, such as severe diarrhea. Additionally, there are insensible losses that are not noticeable but happen continuously. These include processes such as skin evaporation (sweat contains water and electrolytes), breathing, and the excretion of urine and feces[13,14].

In this context, hydroelectrolytic homeostasis, which accurately regulates the body's water and electrolyte balance, is a highly refined process[15]. This is crucial because it affects the condition of all cells in the body[16]. Cells are surrounded by the extracellular fluid (made up of blood plasma and interstitial fluid). Any change in ECF osmolarity can impact cellular volume and structure[12]. Sodium is the main factor determining extracellular fluid osmolarity, as water tends to follow it during movement. This occurs because water easily crosses the cell membrane. Therefore, when ECF osmolarity changes, water shifts between compartments to restore osmotic balance, potentially entering or leaving cells[11,17,18]. There is a physiological set point (near 300 mOsm kg–1) for plasma osmolarity that coordinates the regulation of natriuresis and diuresis. Plasma osmolarity is crucial for maintaining osmotic balance and the volume of body compartments. Significant changes can be very harmful to the body. However, if the variation stays within 1-3%, the body can eliminate excess through renal excretion, sweating, and fecal loss[11].

The global average salt intake (10-15 g of NaCl) is dangerously high, exceeding the World Health Organization's (WHO) guideline[14] of less than 5 grams of sodium chloride (NaCl) per day[1,15,16]. Several factors contribute to increased salt consumption, such as a natural preference for salty flavors[19]. Biological differences in salt perception greatly affect individuals' preferences for and consumption of sodium-rich foods[19]. The availability of processed foods, which are often more affordable, plays a significant role in making them accessible to the entire population[20]. Additionally, biological factors are involved[21] such as sensitivity to salt, which can vary among individuals. There is variation in how people's blood pressure responds to salt, with sensitive individuals being more reactive[22,23].

Guyton proposed a seminal theory explaining how salt intake influences blood pressure in normotensive individuals, attributing this effect primarily to renal mechanisms. According to his hypothesis, impaired pressure natriuresis would lead to

sodium retention and, consequently, sustained increases in arterial pressure[23]. However, hypertension resulting from high sodium intake is now recognized as a multifactorial condition involving dysfunction across multiple physiological systems. Notably, neurogenic mechanisms play a key role in this response. The sympathetic nervous system becomes activated when changes in plasma or cerebrospinal fluid Na^+ concentration are detected. Acute hypernatremia or increased osmolarity stimulates neurons in the rostral ventrolateral medulla (RVLM), thereby elevating arterial pressure[28-29]. These sodium-dependent signals originate from specialized sensory neurons located in brain regions lacking a typical blood–brain barrier. Such circumventricular structures, situated adjacent to the third ventricle and directly exposed to circulating plasma, include sodium-sensitive neurons in the lamina terminalis, which modulate sympathetic outflow through projections to preganglionic neurons in the RVLM[26].

Another way salt increases blood pressure is through interaction with the immune system. High salt intake can stimulate innate immune cells to release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which can act on blood vessels, the kidneys, and the nervous system, increasing blood pressure[24,27]. In the brain, high-salt intake activates microglial cells in the paraventricular nucleus of the hypothalamus. Microglia are the macrophages of the central nervous system and, when activated, release pro-inflammatory cytokines[24].

An increase in cytokines is also observed in the kidneys. In the Dahl salt-sensitive (SS) rat model, excessive sodium intake induces early renal dysfunction characterized by increased expression of pro-inflammatory cytokines and activation of the intrarenal renin-angiotensin-aldosterone system (RAAS), ultimately leading to glomerular and tubular damage[25]. In addition to inducing an increase in blood pressure, salt intake worsens the hypertensive state in pathologies dependent on increased angiotensin II. High salt intake potentiates Ang II-induced oxidative stress in the RVLM, promoting greater sympathetic activation and more severe hypertension. This suggests that pathways such as the SFO–PVN–RVLM axis may be involved, reinforcing the role of the central nervous system in salt-sensitive hypertension[26].

In summary, the rise in blood pressure caused by excess sodium cannot be explained by a single mechanism. It results from the complex interaction among kidney changes, nervous system activation, and immune-inflammatory responses, which

together maintain high blood pressure. The complexity emphasizes the need for an integrated approach to understanding and managing it.

1.2 Renovascular Hypertension

The World Health Organization (WHO) defines a hypertensive state as systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg. Hypertension is a chronic global health problem responsible for over 10 million deaths each year. The prognosis for people with hypertension is poor because the increase in blood pressure is usually silent, which delays diagnosis and treatment. About 4 out of 5 people with hypertension do not have their condition under control, leading to higher death rates from cardiovascular diseases[27,28].

High blood pressure is categorized as either primary or secondary, with primary hypertension being the most common. The etiology of primary hypertension is multifactorial and is usually associated with genetic and environmental factors, without a defined cause. Secondary hypertension, however, has a defined cause and is potentially reversible[26,27]. The most common form of secondary hypertension is renovascular. In this case, high blood pressure results from an obstruction in one or both renal arteries. Any clinical condition that reduces perfusion pressure to the kidney can increase systemic blood pressure, but the two leading causes are atherosclerosis (90%) and fibromuscular dysplasia (10%)[29]. Patients with renal obstruction due to atherosclerosis tend to be older and have systemic atherosclerotic plaques[30]. These individuals often have a history of smoking, hyperlipidemia, obesity, and diabetes mellitus. Fibromuscular dysplasia, caused by thickening of the arterial wall due to abnormal growth of arterial wall cells, primarily affects young women (< 30) who smoke [31].

Goldblatt, in 1934[32], developed a technique called 2-kidneys-1-clip (2K1C) to simulate renal artery obstruction. In unilateral renal artery stenosis, the glomerular cells in the juxtaglomerular apparatus detect a drop in renal perfusion. The kidney with the obstructed artery begins to secrete renin in response to renal ischemia. Renin is an enzyme that interacts with the liver-derived protein angiotensinogen to produce angiotensin I, an inactive peptide, which is converted into angiotensin II (ANG II) by the angiotensin-converting enzyme (ACE), which is expressed across the vascular endothelium, with a markedly higher contribution of the lungs[33]. The study by

Johansson et al[34], conducted in humans, showed that plasma renin and sympathetic efferent nerve activity increase during renovascular hypertension. The same findings are observed in animal studies[35,36].

Angiotensin II is a hormone that constantly participates in the regulation of blood pressure. Its actions can occur through its binding to the AT1 receptor in the peripheral or central systems. Peripherally, it causes vasoconstriction, increased sodium reabsorption in the kidneys, and the release of aldosterone by the adrenal glands[30]. Plasma ANG II reaches the brain through circumventricular organs (CVOs), which are central nuclei lacking the blood-brain barrier. These areas are rich in AT1 receptors, and when activated, they stimulate thirst, sodium appetite, vasopressin release, and sympathetic nervous system activation[37].

After 2K1C surgery, systolic blood pressure begins to increase from the 13th day onward, stabilizing at the end of the sixth week. In the first 4 weeks after surgery, the rise in blood pressure was initially attributed to elevated renin levels and increased circulation angiotensin II (ANG II). During this time, changes in baroreflex sensitivity were also noted. Starting from 28 days post-surgery, hypertension increasingly exhibited a neurogenic component, characterized by heightened sympathetic activity[35,36]. However, it was later demonstrated that sympathetic hyperactivity arises before the increase in blood pressure in the 2K1C model, suggesting an early neurogenic component[38].

The increase in sympathetic activity in this model can be caused by several pathways. One of them is through an increase in the production of oxidative stress. Reactive oxygen species are generated by the binding of angiotensin II (ANG II) to AT_1 receptors. This activation enhances the expression of NAD(P)H oxidase subunits in the rostral ventrolateral medulla (RVLM), leading to greater superoxide production and consequent sympathetic activation[39,40].

Evidence suggests that 2K1C hypertension is partly driven by a persistent, low-grade inflammatory state, occurring both in peripheral tissues and within the central nervous system. Systemic administration of pentoxifylline (a TNF-alpha synthesis inhibitor) immediately after 2K1C surgery and for sixty days attenuates the development of 2K1C hypertension[41]. The drug's effect was also observed centrally, with reduced sympathetic activity and microglial activation in areas such as the PVN and RLVM[41]. The commissural nucleus of the solitary tract (cNTS) is also involved in the development of 2K1C hypertension. Previous data from our laboratory showed

increased expression of microglia, astrocytes and pro-inflammatory cytokines in this region[42]. Furthermore, injecting losartan into the cNTS reduces blood pressure in these animals, demonstrating the action of ANG II in this area[42]. During the 3rd and 4th weeks after inducing renovascular hypertension, 2K1C animals show disruption of the blood-brain barrier in regions such as PVN, the RVLM, and the nucleus of the solitary tract (NTS), which facilitates access for the circulating ANG II to these areas [34-36]. Central ANG II promotes barrier disruption, increased intracranial pressure, and loss of cerebral compliance[43-45].

Renal dysfunction is also present in the 2K1C model. Chronic renal hypoperfusion promotes the recruitment and accumulation of inflammatory cells within the clipped kidney[46]. Kidney inflammation is directly associated with the actions of intrarenal ANG II, which, once inhibited, reduces local inflammation[47]. The brain receives signals from the kidneys. Afferent sensory fibers from the kidney connect to areas of the brainstem, such as the PVN and RVLM[48]. Increased kidney inflammation is one of the stimuli for these fibers, which can lead to increased sympathetic activity[49].

In summary, renovascular hypertension results from the interaction between over-activation of the RAAS, increased sympathetic activity, and renal and central inflammatory processes. In the 2K1C model, ANG II acts as a central element by promoting vasoconstriction, sodium retention, neuroinflammation, and disruption of the blood-brain barrier. Inflammation of the clipped kidney also sends afferent signals that amplify the sympathetic response, maintaining hypertension. Thus, the integration between the kidney, central nervous system, and ANG II is essential to understanding the pathophysiology of the disease and guiding more effective therapeutic interventions.

5 CONCLUSIONS

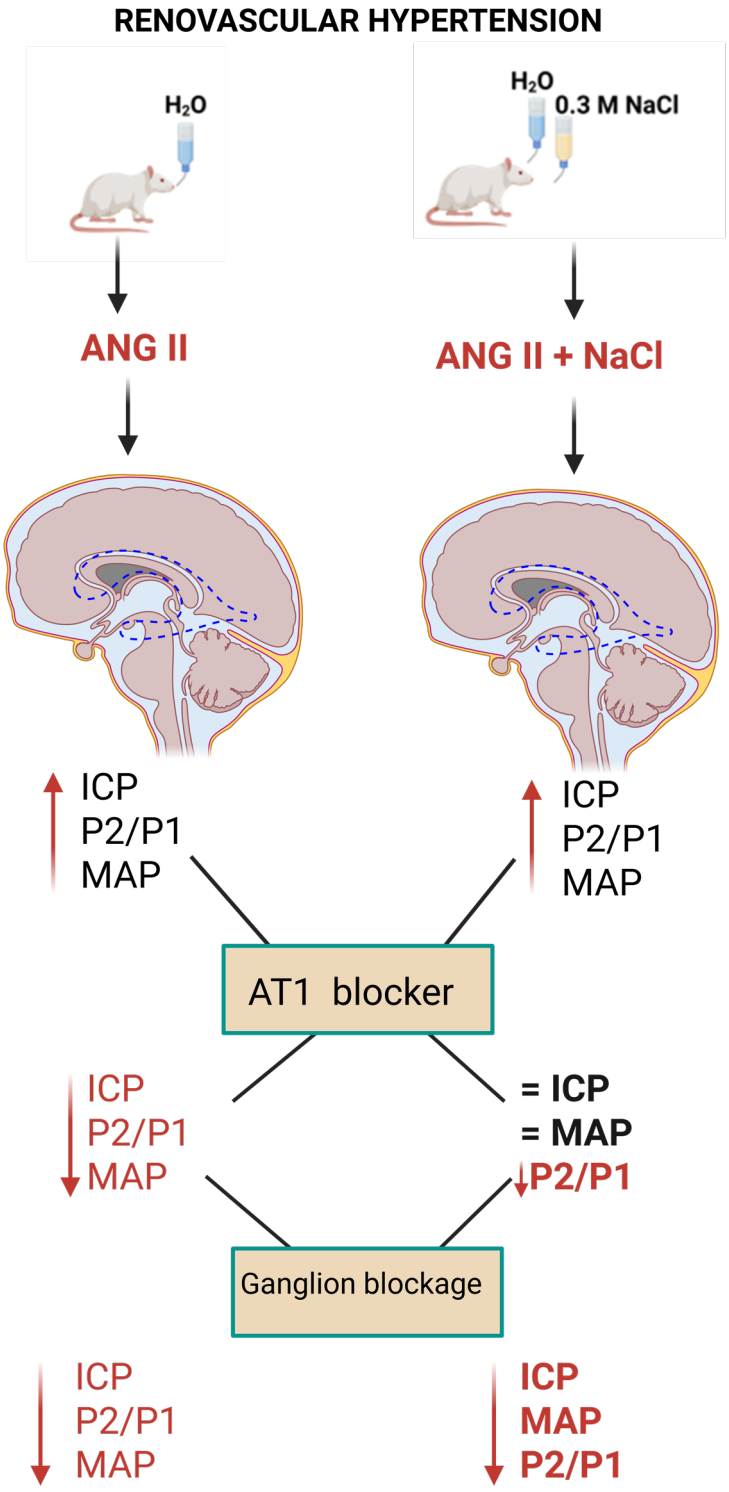
The findings presented in this thesis provide novel insights into the mechanisms linking angiotensin II (Ang II) signaling, sodium intake, and the development of brain and kidney dysfunction in renovascular hypertension (RVH). Collectively, the results demonstrate that Ang II-mediated neuroinflammation and renal remodeling are central components of RVH pathophysiology and that these processes are modulated by sodium homeostasis.

The data revealed that short-term blockade of AT_1 receptors with losartan effectively reduced mean arterial pressure and reversed glial activation in key autonomic nuclei, such as the nucleus of the solitary tract (NTS). These findings confirm the pivotal role of Ang II in promoting microgliosis and astrogliosis within the brainstem. However, persistent inflammation in the area postrema, even after losartan treatment, indicates the involvement of Ang II-independent pathways.

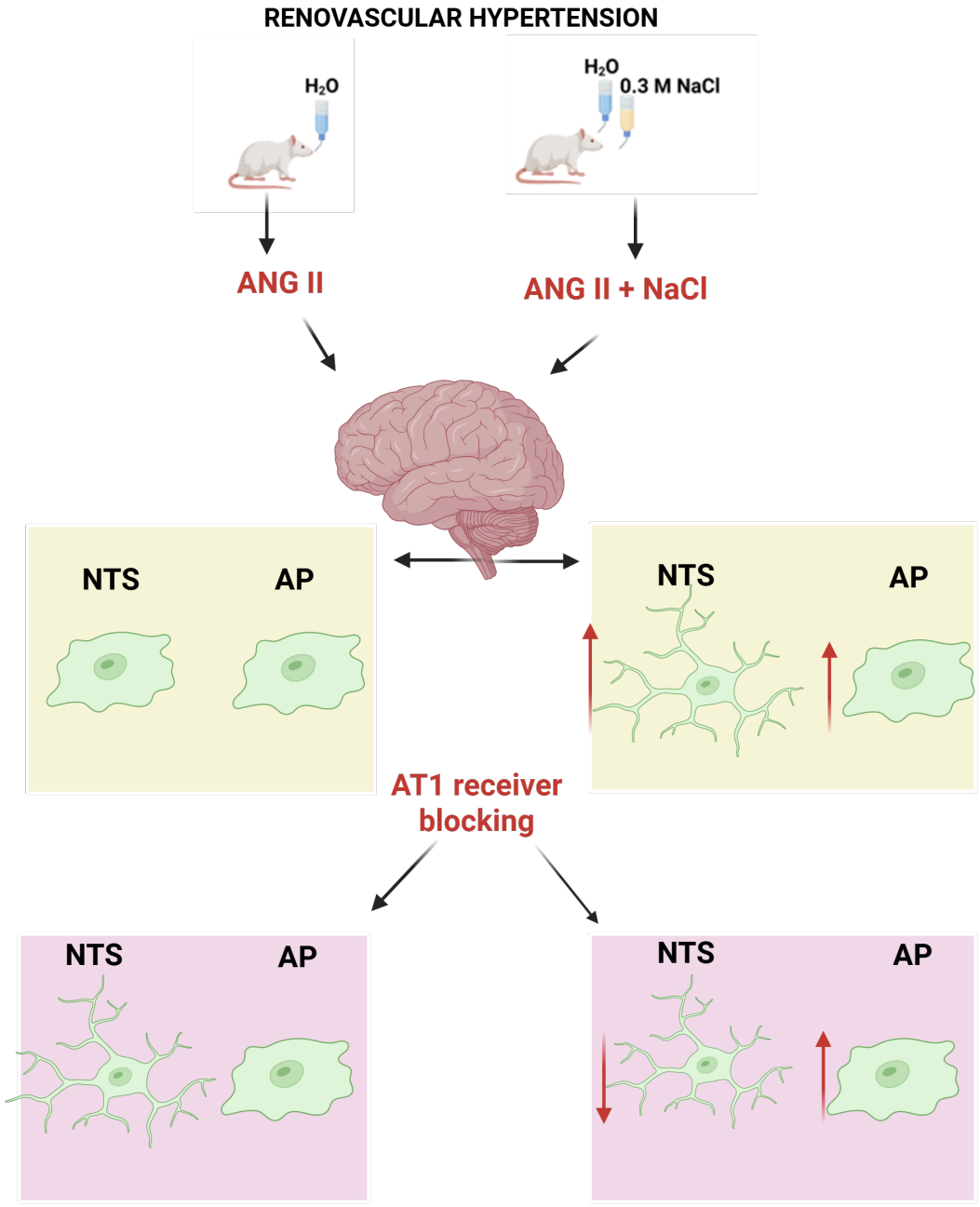
At the renal level, losartan improved glomerular morphology and reduced cellular reactivity, although established fibrosis remained unchanged, suggesting that longer therapeutic interventions are required to achieve full structural recovery. Importantly, salt intake decreases losartan's ability to normalize arterial pressure and intracranial parameters, yet without worsening renal fibrosis.

Together, these findings reinforce the concept that the interplay between RAAS overactivity and sodium excess contributes to the progression of neurovascular and renal damage in RVH. Therapeutic strategies that simultaneously target RAAS activation, neuroinflammation, and sodium balance may offer more effective control of resistant hypertension and prevent long-term end-organ injury. Below is a schematic summary of the main findings in manuscripts 1 and 2.

Manuscript 1:



Manuscript 2:



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