ECCM 2021

MDPI

Proceedings

Effect of Potassium Intake on the Regulation of the ENaC Renal Epithelial Channel in Primary Arterial Hypertension: A Systematic Review †

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† Presented at the 1st International Electronic Conference on Clinical Medicine, 15–30 September 2021; Available online: https://eccm.sciforum.net/.

Abstract: The balance between sodium and potassium represents a key point for the regulation of hypertension and in recent years, scientific research has contributed to its understanding from molecular to epidemiological aspects. This review aims to show evidence of regulation of the ENaC channel by the intake of potassium for the control of primary hypertension. The epithelial sodium channel -ENaC- regulated by the renin-angiotensin-aldosterone system at the renal level, is essential for sodium homeostasis and the maintenance of arterial hypertension, and several medical investigations have generated drugs that inhibit activation pathways for sodium action on blood pressure; also, observational, interventional and experimental studies in humans and animals demonstrate the consequences of increased sodium intake. In this context, potassium intake is suggested as a more comprehensive treatment for the control of arterial hypertension, acting at the molecular level with decreased activation of the ENaC channel by normalizing sodium and potassium concentrations, reducing sensitivity to the development of cardiovascular diseases; Moreover, nutritional evidence shows that populations with natural foods rich in fruits and vegetables that exceed potassium intake (150 mEq per day) and minimize sodium intake (20–40 mEq per day) suffer arterial hypertension at a rate of less than 3%, without negative effects on lipid balance, catecholamines, and ion concentrations in the kidney.

Keywords: arterial hypertension; ENaC channel; sodium and potassium balance; nutrition

Citation: Torres-Benítez, A.; Lascano-Torres, F. Effect of Potassium Intake on the Regulation of the ENaC Renal Epithelial Channel in Primary Arterial Hypertension: A Systematic Review. **2021**, *68*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s):

Received: date
Accepted: date
Published: date

1. Introduction

The Primary arterial hypertension, defined as sustained systolic and/or diastolic pressure above 140/90 mmHg [1], is a major risk factor for chronic non-communicable diseases that cause vascular damage, disability and/or death [2], with increasing prevalence and incidence figures associated mainly with the consumption of processed and/or treated foods with high levels of sodium chloride, sedentarism, and obesity [3]. In the last 20 years, the Mosaic theory of hypertension proposed by Page in 1960, which brought together environmental, genetic, neuronal and hormonal interactions, has been replaced by genomic and molecular studies of the regulatory pathways of blood pressure control leading to the development of more specific drugs without side effects [4]. In this scenario, the role of sodium has been widely studied, taking into account that it is one of the cations involved in sustaining the osmolarity of extracellular fluid and is regulated mainly by the renin-angiotensin-aldosterone system (RAAS) at the renal level, which under a diet rich in salt should be suppressed under normal conditions [5]. Despite the variety of tolerance of various populations to dietary sodium intakes, its imbalance and massive consumption

activate the molecular action of the sodium channel in the distal tubule of the kidney, to be decisive in the adaptation to salt and the pathogenesis of arterial hypertension [6].

On the other hand, with this disease, there is a substantial decrease in potassium levels in the body, due to altered sodium-potassium compensation, which stimulates the sodium exchangers, increases intracellular acidosis, and activates the sympathetic nervous system and the RAAS [7]. Hypertension is also seen as a risk factor for morbidity and mortality that has been treated by various drugs, such as RAAS blocking agents, diuretics and other specific inhibitors, working with therapeutic strategies that lead to the normalization of potassium in patients at high cardiovascular risk, with randomized and controlled cohorts that demonstrate the efficacy and safety of the consumption of this ion [8], as well as in murine models that are strongly sensitive to the effects of increased sodium and potassium depletion [9] in their diet, and through potassium intake tests, hypertensive levels due to high salt loads are reduced and the survival of the animals under study is prolonged [10]. Clinical evidence also shows that habitual sodium intake increases systolic pressure by an average of 6 mmHg and diastolic pressure by 4 mmHg in normotensive subjects, and in hypertensive subjects, systolic pressure increases by an average of 7 mmHg and systolic pressure by 6 mmHg; Conversely, potassium supplementation for hypertensive subjects reduces systolic pressure by an average of 4.4 mmHg and diastolic pressure by 2.5 mmHg; in normotensive subjects, the variation is minimal [2,5,11].

2. Methods

A literature search was performed until March 2021 in the databases WoS, Scopus, ScienceDirect, and PubMed, using the keywords: arterial hypertension, ENaC channel, sodium-potassium balance. References from relevant review articles were also identified, as well as others registered in the section of similar articles in PubMed.

3. Results and Discussion

In the physiopathology of hypertension, a relationship has been described between salt intake and activation of the renal epithelial channel ENaC for reabsorption of filtered sodium together with increased activity of stimulant systems [12], due to the reduction in potassium concentrations and the need to maintain cell tonicity and volume[2]. Public health strategies for the control of hypertension have been aimed at reducing salt intake [13], however, the current Western diet limits this change and proposes an increase in potassium consumption, as it constitutes the most abundant intracellular cation in the body, and an alteration in its homeostasis influences the appearance of cardiovascular diseases [14]; also, nutritional evidence shows that populations with natural foods, rich in fruits and vegetables that exceed potassium (150 mEq per day) and minimize sodium (20–40 mEq per day), suffer from arterial hypertension at a rate of less than 3% and a potassium-sodium balance greater than 3 [15]. Therefore, it is hypothesized that the intake of potassium regulates the activation of the renal epithelial channel ENaC for sodium reabsorption in an in vivo model of primary arterial hypertension.

First, during arterial hypertension, sodium reabsorption occurs through the renal ENaC channel and potassium secretion through the ROMK channel, which generates a more negative voltage in the luminal membrane, with an alteration of the sodium-potassium ATPase pump due to high and prolonged salt intake [2]; secondly, it was recently reported that the stimulation of the ENaC channel does not necessarily derive from the traditional action of the mineralocorticoid (MR) receptor, but rather involves a new mechanism of stimulation mediated by angiotensin II receptor independent of MR activated by aldosterone [16]. Based on these postulates, it is proposed that the intake of potassium in a model of primary arterial hypertension increases intracellular potassium levels and reduces hypertension, through the stability of the basolateral sodium-potassium ATPase pump that transports potassium into the cell and sodium out of it in a ratio of 2:3; the normalized mobility of the ions by the adjusted concentration of both, reduces the acidosis

by the low stimulation of the RAAS, and in the absence or reduction of angiotensin II and/or aldosterone, the expression and action of the ENaC channel and a parallel activated proton exchanger are decreased.

Currently, models of rats with high blood pressure are used that, when subjected to experimental protocols with concentrations of 4% or 8% NaCl, stimulate an increase in blood pressure. However, they resort to inhibiting components of the RAAS using knockout mice for the renin gene that decreases the activity of ENaC [8]. Alternatively, the concentration of different concentrations of potassium administered to hypertensive rats, would allow evidence of the levels of variation in systolic and diastolic pressure, and assume optimal levels of potassium intake in animals that evolve to normal blood pressure. Various epidemiological studies show that daily potassium intake (90–120 mmol/day) reduces blood pressure and subsequent risk of stroke [17,18].

The perspectives in the study of the action of the ENaC channel on the control of primary arterial hypertension continue with experimentation on experimental models of renal syndromes associated with cardiovascular diseases [19]. Similarly, more than basic scientific research, the implementation of health policy in the face of increased doses of potassium in food does not have negative effects on the balance of lipids, catecholamines, and ion concentrations in the kidney [17].

4. Conclusions

The balance of the sodium/potassium ratio that should exist in our diet is a reality [2]. It is worth recognizing the question: ¿is it possible to return to the state of our ancestors with a healthy diet, rich in vegetables and fruits, for the prevention and primary treatment of high blood pressure? the answer is on everyone's table every day. Daily salt intake will be significantly associated with the development of hypertension [20], therefore potassium intake can be introduced as a change that activates the molecular mechanism of ion regulation and cardiovascular disease susceptibility.

Author Contributions: All authors contributed equally to this work. All authors discussed the results and implications and commented on the manuscript at all stages. A.T.-B. and F.L-T. wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: Please add: This research was funded by CONICYT PFCHA/National Doctorate Scholarship/2357-2021 (A-T.-B.).

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: A.T.B. expresses his gratitude to Dra. Claudia Torres, Dra. Natalia Méndez and Dr. Diego Halabi for their guidance in writing this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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