PERSPECTIVES IN HYPERTENSION

When sodium meets potassium: a systems model of blood pressure control

ANITA T. LAYTON

Department of Applied Mathematics, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
Department of Biology, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
Cheriton School of Computer Science, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
School of Pharmacology, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada

Sodium and potassium are often discussed separately when we think about blood pressure regulation, but in physiology, they are constant partners. Their interplay shapes renal handling of electrolytes, extracellular fluid volume, and ultimately arterial pressure. In our recent paper "Modulation of blood pressure by dietary potassium and sodium: sex differences and modeling analysis" (Stadt & Layton, 2024),[1] we developed a computational model that brings these elements together in a single, integrated framework. By linking sodium and potassium homeostasis with fluid balance, hormonal regulation, and blood pressure control, and by incorporating sex-specific physiology,[2,3] we can explore how dietary changes in sodium and potassium intake interact to influence blood pressure.

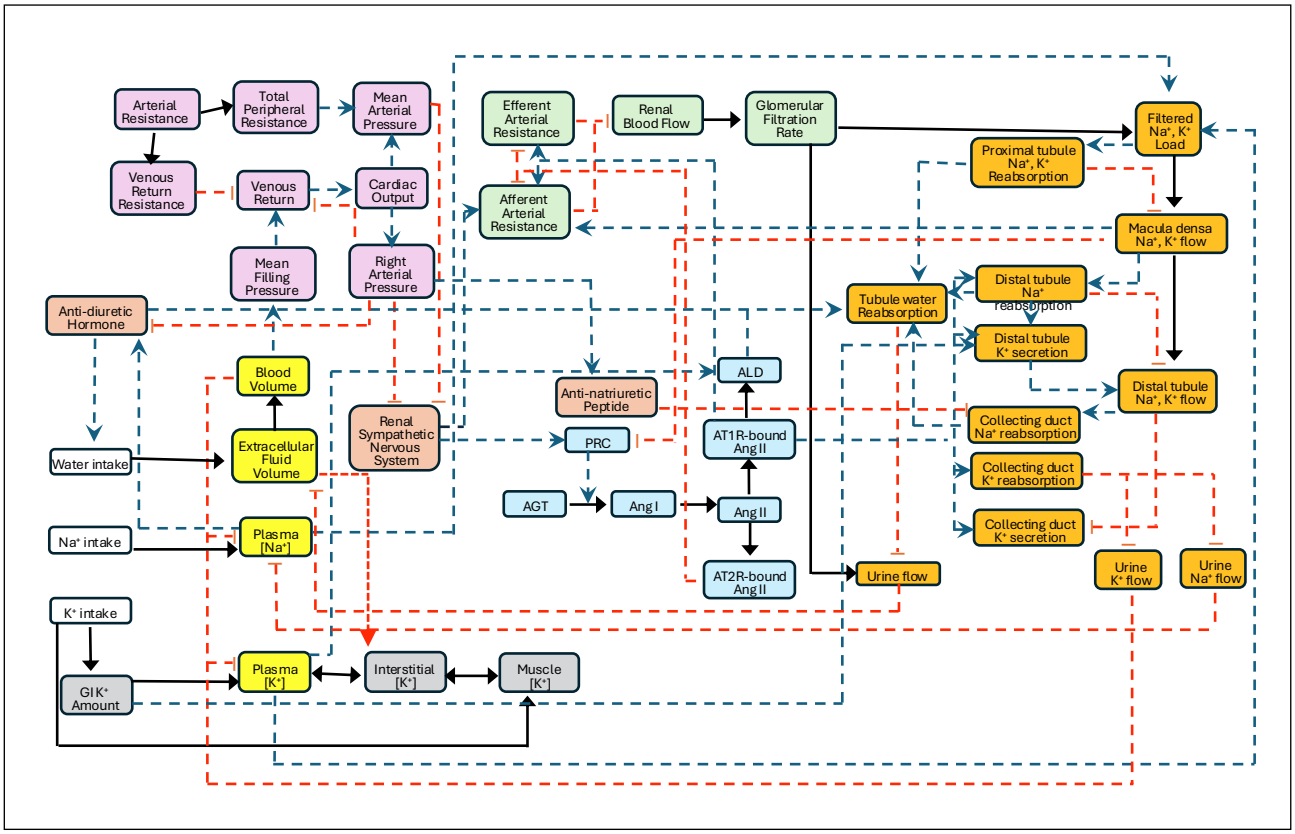
Overview of the Model

The model is a whole-body, sex-specific representation of sodium, potassium, and fluid homeostasis, linked to blood pressure. Its goal is to capture the integrated physiology of kidney function, hormonal control, and cardiovascular response so that we can examine how changes in dietary sodium and potassium intake affect blood pressure.

At the renal level, the model represents glomerular filtration, tubular reabsorption and secretion of sodium and potassium along multiple nephron segments, and their regulation by hormones such as aldosterone and angiotensin II. It also includes gastrointestinal feedforward control of potassium excretion – signals that are activated by oral potassium intake before plasma [K^+] rises significantly – which helps prevent large postprandial fluctuations. The cardiovascular component links extracellular fluid volume to arterial pressure, allowing us to capture the long-term blood pressure effects of altered sodium and potassium handling. Importantly, the model incorporates male–female differences in renal transporter abundance and hormone levels, which enables simulations of sex-specific responses.

How does one build a computational model to describe the interactions among these regulatory processes? **Figure 1** shows a schematic diagram of how the model represents physiological feedback/feedforward mechanisms that regulate blood pressure and potassium homeostasis. The model diagram is highly intricate and not easy to untangle, not unlike the underlying physiological system, with many interacting components. There are positive and negative feedback signals (denoted by blue and red dashed lines) going in all kinds of directions, linking the renal system (orange boxes), cardiovascular system (purple boxes), gastrointestinal system (a grey box), renal sympathetic nervous system (a beige box), and renin-angiotensin-aldosterone system (blue boxes). The complexity of the system is precisely why computational modeling is an asset in data interpretation.

Figure 1. Model schematic diagram depicting physiological feedback/feedforward mechanisms that regulate blood pressure and potassium (K+) homeostasis. Box colors indicate processes or variables that are more closely related to each other. Solid arrows show the sequence of steps in a process, or one variable that turns into another. Blue and red dashed lines indicate simulating or inhibiting actions. Modified from Ref.[1] with permission.



This model is the result of integrating two lines of previously published work. The first is the series of computational models we published on sodium, fluid, and blood pressure regulation.[4,5] These models represent the renin-angiotensin-aldosterone system, pressure natriuresis, and the links between sodium balance, extracellular volume, and arterial pressure. The second body of work is our models of potassium homeostasis,[6–8] which represent dietary intake, gastrointestinal feedforward signals, cellular uptake (via insulin- and aldosterone-sensitive Na^+-K^+-ATPase), and renal potassium excretion, including both feedback and feedforward regulation.

By combining these two frameworks, we were able to represent not only the regulation of sodium and potassium individually but also their physiological interactions. This integration was essential, because potassium intake does not simply alter plasma [K^+], it also affects sodium handling, extracellular volume, and ultimately blood pressure.

Sex differences were incorporated based on experimental data for transporter expression and hormone levels, providing separate male and female parameter sets.

Simulation Results, Key Findings, and Implications

We used the model to simulate a range of dietary scenarios: high and low sodium intake, high and low potassium intake, and combinations of the two. Several consistent patterns emerged. High sodium intake predictably increases extracellular fluid volume and raises arterial pressure, whereas high potassium intake has the opposite effect: it stimulates kaliuresis but also promotes natriuresis by reducing proximal tubular sodium reabsorption and enhancing distal sodium delivery. The resulting natriuresis reduces extracellular fluid volume and lowers blood pressure. Combined high sodium and high potassium intake demonstrates that the potassium effect is robust – potassium supplementation attenuates or even reverses

sodium-induced blood pressure elevations. Finally, sex differences were apparent: female transporter patterns produced a blunted hypertensive response to sodium loading and slightly different patterns of kaliuresis and natriuresis with potassium supplementation. These results are summarized in **Figure 2**.

These findings align with clinical and experimental evidence that dietary potassium can mitigate the hypertensive effects of sodium[9,10] and support recommendations to increase potassium intake (e.g., through fruits and vegetables) as part of blood pressure management strategies.

Here are a few clinical implications of our findings:

- Potassium supplementation is an effective antihypertensive strategy even in the presence of high sodium intake, not only because of direct kaliuresis but also because of its secondary natriuretic effect.
- Sex differences matter. Women may have a more attenuated blood pressure response to sodium load, which has implications for dietary guidelines and for interpreting clinical studies.
- Integrated modeling is powerful. By linking renal transport, hormonal regulation, and cardiovascular responses, we can explore "what-if" scenarios that are difficult to test experimentally.

Limitations and Next Steps

As with any model, there are limitations. Human data for some parameters – particularly transporter abundances and hormonal regulation in females – remain sparse. Some regulatory mechanisms, such as gut-to-kidney signaling of potassium intake, are incompletely characterized experimentally. In addition, the model is designed for long-term (hours to days) regulation and does not represent rapid, minute-to-minute changes, nor does it yet include pathological states such as chronic kidney disease.

Future work could expand the model to include disease conditions, aging, circadian variation, and inter-individual variability. Such refinements could make it even more useful for predicting blood pressure responses to dietary interventions in specific patient populations.

Conclusion

This work shows what happens when sodium meets potassium – not just in the nephron, but across the whole system. By integrating sodium and potassium handling with fluid and blood pressure regulation, our model highlights how these two ions jointly shape long-term cardiovascular outcomes. The simulations reinforce what clinical data have suggested: raising dietary potassium can offset the hypertensive effects of sodium, and sex-specific physiology

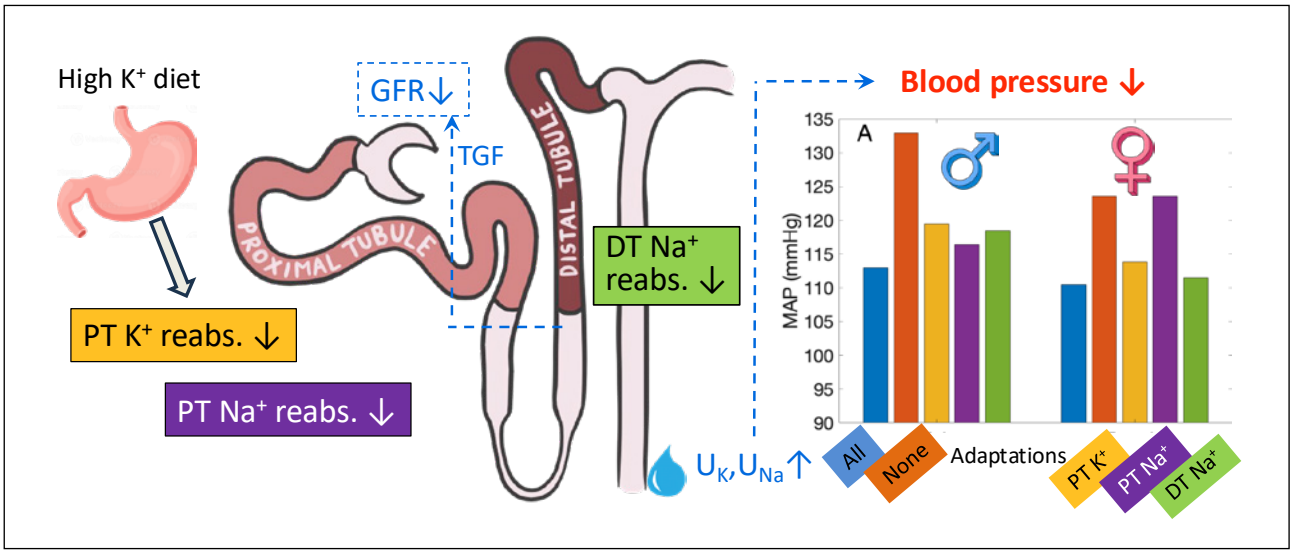


Figure 2. High potassium (K+) intake lowers blood pressure by suppressing renal K+ and sodium (Na+) reabsorption. In males, reduction in proximal Na+ transport has the largest effect. In females, where Na+-Cl- cotransporter activities are higher, reduction in distal Na+ transport has the largest effect. PT, proximal tubule; GFR, glomerular filtration rate; TGF, tubuloglomerular feedback; DT, distal tubule; UK, urinary K+ excretion; UNa, urinary Na+ excretion. Reproduced from Ref[1] with permission.

matters for understanding blood pressure responses. Bringing sodium and potassium into the same modeling framework gives us a clearer, mechanistic picture of blood pressure control, one that can inform future research, refine dietary recommendations, and ultimately improve patient care. Last but not the least, this work underscores the value of computational modeling as a tool for exploring complex, multiorgan physiology and for generating mechanistic insights that can inform dietary recommendations and guide future research.

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Anita T. Layton – anita.layton@uwaterloo.ca