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Diuretics work differently according to biological sex and time of treatment, shows study

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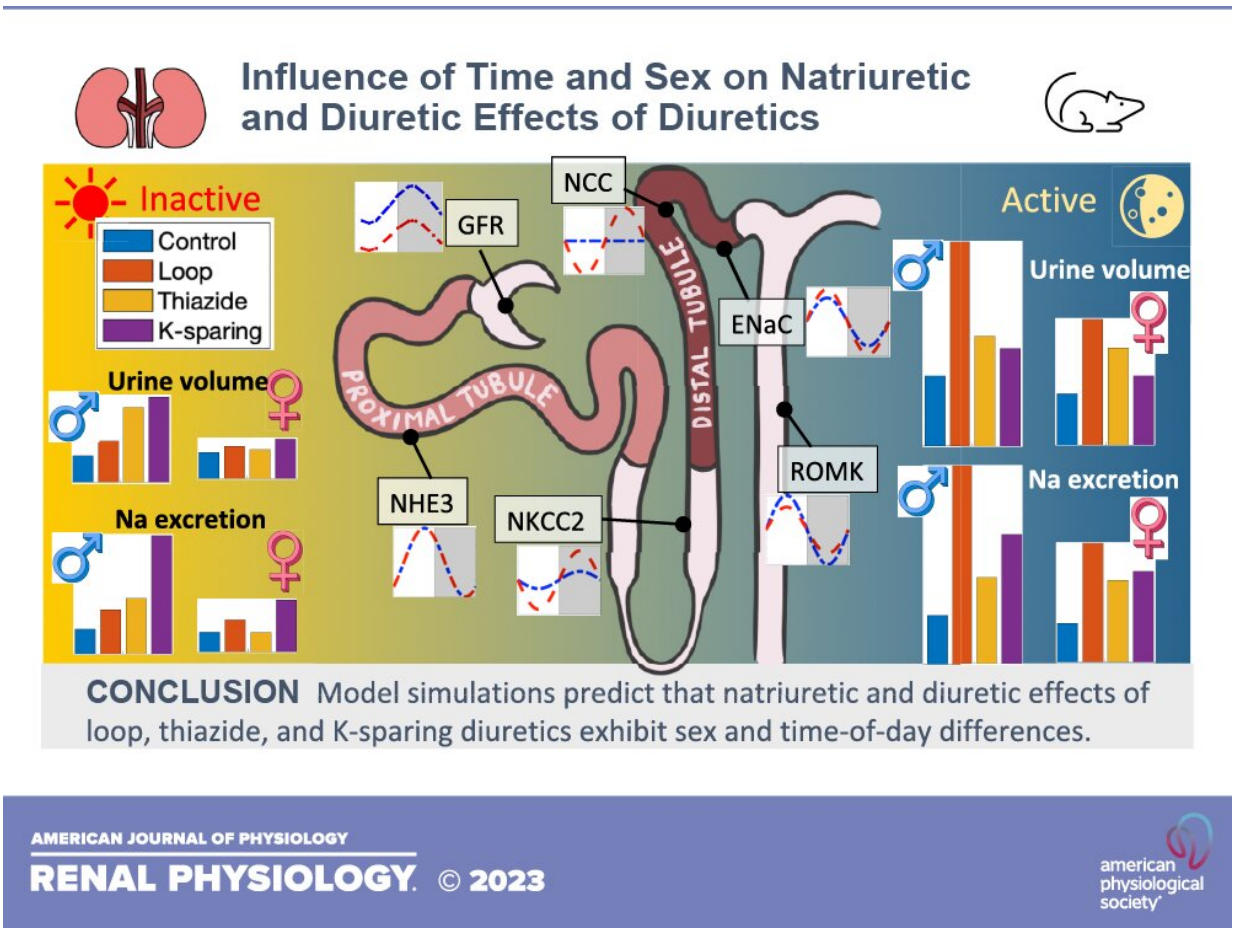

Abstract. Credit: *American Journal of Physiology-Renal Physiology* (2023). DOI: 10.1152/ajprenal.00296.2022

A new computational study in a mouse model finds biological sex and time of day makes a difference in the effectiveness of diuretics—medications commonly prescribed to manage high blood pressure. The study is published ahead of print in the *American Journal of Physiology-Renal Physiology*.

The body's circadian clock and biological sex are two key factors in blood pressure management. In most people, blood pressure is highest in the morning and dips lower at night. Nondippers—the term coined for people whose blood pressure does not significantly drop overnight—have higher risks of chronic high blood pressure and heart disease. The kidneys play a significant role in blood pressure regulation by managing fluid and electrolyte levels in the body. The body's circadian clock also regulates kidney function.

In a new study, researchers explored how time of day and biological sex affect how well diuretic medications work. These drugs act on different renal transporter proteins to increase the amount of urine the body excretes.

The research team used computational models of cells from male and female mouse nephrons—the functional unit of the kidneys—to examine the effects of three types of diuretics:

- Loop diuretics inhibit the sodium-potassium-chloride co-transporter.
- Thiazide diuretics inhibit the sodium/chloride cotransporter.
- Potassium-sparing diuretics inhibit the epithelial sodium channel and increase urine flow without causing potassium loss in the urine.

The research team's simulations represented active (nighttime) and inactive (daytime) cycles of a mouse's circadian rhythms. They found

that in both sexes, loop diuretics were predicted to cause higher levels of urine output and sodium excretion during the active phase. There was very little change in urine output in females with thiazide diuretics but a marked increase in both urine volume and sodium excretion in males.

Treatment with potassium-sparing diuretics was found to cause substantially higher urine volume and sodium excretion during the active phase in females but not as much in males compared to the other diuretics.

Because the human active/inactive cycle is typically opposite from that of rodents—most people are awake during the day and asleep at night—kidney function and urine output tends to be highest in people during the day.

Based on the findings of this study and previous research, the researchers explained that changing when people take blood pressure medications—in the evening instead of the morning, for example—may make the treatment more effective. "Chronotherapy, i.e., tailoring drug administration time to match the body's diurnal rhythms to increase the drug effect, can play a major role in improving modern personalized medicine," the researchers wrote.

"Influence of administration time and sex on natriuretic, diuretic and kaliuretic effects of diuretics" is published ahead of print in the *American Journal of Physiology-Renal Physiology*.

More information: Pritha Dutta et al, Influence of administration time and sex on natriuretic, diuretic, and kaliuretic effects of diuretics, *American Journal of Physiology-Renal Physiology* (2023). DOI: 10.1152/ajprenal.00296.2022

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