

# Females use anti-inflammatory T cells to keep their blood pressure down

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In the face of a multipronged front to drive blood pressure up, including a high-salt diet, females are better able to keep their pressure down by increasing levels of a T cell that selectively dials back inflammation, scientists say.

Females have an innate ability to upregulate these anti-inflammatory cells, called Tregs, in response to a challenge, says Dr. Jennifer C. Sullivan, pharmacologist and physiologist, noting that the cell's levels are known to increase to help maintain a healthy pregnancy, for example, so the [immune system](#) does not attack the fetus, which has DNA from both parents.

"This is just a different challenge, but we are using those same protective pathways to do something else good for us," says Sullivan, professor in the Department of Physiology at the Medical College of Georgia at Augusta University, who studies [sex differences](#) in hypertension, the so-called 'silent killer' that is a key risk factor for [heart disease](#) and stroke.

Tregs are known to help protect us from an

excessive immune response, like the cytokine storms causing so much destruction in COVID-19, as well as [autoimmune diseases](#) like rheumatoid arthritis, where our immune system attacks our own tissues, and are naturally associated with lower [blood](#) pressures and less organ damage.

Sullivan's most recent work, published in the journal *Hypertension*, supports the hypothesis that [females](#) rely heavily on Tregs for [blood pressure control](#) and this mechanism accounts for at least one of the sex differences in that control, she and her colleagues write.

Females, at least before menopause, tend to have lower blood pressures than males. "We think, based on studies in this and other models, that the ability of the female to maintain or upregulate those T regulatory cells is critical to their ability to maintain a lower pressure," she says.

"It's a compensatory response to an increase in blood pressure to help the overall cardiovascular impact," Sullivan says of this innate ability that could provide a promising new hypertension treatment strategy, particularly for females.

That compensatory role held when they turned Tregs down in this rapid hypertension-evoking environment called DOCA salt treatment in rats. When they used a neutralizing antibody to prompt about a 30-40% reduction in the number of Tregs, blood pressure went up in the females, essentially matching the measures found in the males. Sullivan suspects males and females likely make similar numbers of Tregs—they have found similar numbers in the spleen, for example—but differences may be in the recruitment and proliferation to organs key to blood pressure control like the kidneys, one reason she wanted to look specifically at Treg levels there.

Both sexes actually experienced increases in pro-inflammatory T cells, which contribute to infection fighting. Blood pressure increased significantly in

both sexes by day two, but by the end of 21 days of treatment, male blood pressures were significantly higher. And, females experienced significantly more of the blood pressure-mitigating Tregs along with their lower pressures, the scientists report.



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When given therapy to deplete Tregs, it essentially equalized Treg levels in the males and females but it significantly increased blood pressure only in females. The fact that decreasing Tregs in males did not affect blood pressure may indicate that male blood pressure is not as dependent on this mechanism during normal conditions, they write. However the clear impact in females supports the hypothesis that females are "highly dependent" on Tregs to maintain their blood pressure, they also write.

The hormone DOCA, or deoxycorticosterone acetate, prompts the kidneys to hold onto both more sodium and water, so there is a higher fluid volume in the blood vessels, which drives up blood pressure. Then, as with some humans, a [high-salt diet](#) magnifies the problem and so does the removal of a single kidney. This DOCA-salt model is a commonly used hypertension model, which provides scientists a good window for when hypertension sets in.

While they expected that like blood pressure, kidney damage also would be less in females

in reality kidney damage was comparable in the sexes. While they are not yet certain what the surprise finding means, they are exploring ideas like protecting the kidney structure is simply not something Tregs do. Still they have found in similar studies in other rat strains, that kidney protection was afforded, and that in these new studies, even with significant blood pressure reductions in the females, blood pressures in both sexes were comparatively high compared with normal, so kidney damage may still result. They note that when they reduced Treg levels in females, which drove blood pressure up, it did not increase kidney damage further and investigators say more work needs to be done to understand what appear to be conflicting findings.

"If we can better understand how and why females are increasing their Tregs that could lead to therapies, potentially for both sexes, to also avoid or treat high-inflammation conditions like autoimmune and cardiovascular disease," Sullivan says. In fact, autologous Treg therapy is already showing promise in conditions where excessive inflammation is a factor like Crohn's disease and type 1 diabetes.

For about a decade, scientists have been really interested in the immune system's control of blood pressure and the role of T cells in that control. Sullivan's lab did some of the early work looking specifically at calming Tregs. They have found, for example, in the spontaneously hypertensive rat model, the most commonly used hypertension model, that Tregs were "one of the most pronounced sex differences we saw between the males and females and it tracked most faithfully with changes in blood pressure," she says. They also saw that when a female's blood pressure goes up, so do her Treg levels, and those immune cells decrease when blood pressure does.

Normal blood pressure numbers also indicate sex differences. Generally women have lower blood [pressure](#) than men of a similar age; the advantage appears mostly lost after menopause when female pressures can creep even higher than males'.

Hypertension is the most common risk factor for

cardiovascular disease, causing 18 million deaths a year, the investigators write, however mechanisms controlling [blood pressure](#) in either sex remains largely unknown. Genetic, dietary and environmental factors, like sodium intake and stress levels respectively, are considered causative.

Sullivan's laboratory has ongoing studies looking further at production of the anti-inflammatory cells, including the role of the short-lived gas and powerful blood vessel dilator nitric oxide, which has been associated with increased Treg levels in females. Estrogen increases nitric oxide production.

Sullivan reported last year that a high-fat diet also increased inflammation-promoting T cells and decreased inflammation-dampening Tregs in both sexes, but the females maintained higher percentages, just as they do normally.

**More information:** Kasey M. Belanger et al. Greater T Regulatory Cells in Females Attenuate DOCA-Salt-Induced Increases in Blood Pressure Versus Males, *Hypertension* (2020). DOI: [10.1161/HYPERTENSIONAHA.119.14089](https://doi.org/10.1161/HYPERTENSIONAHA.119.14089)

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