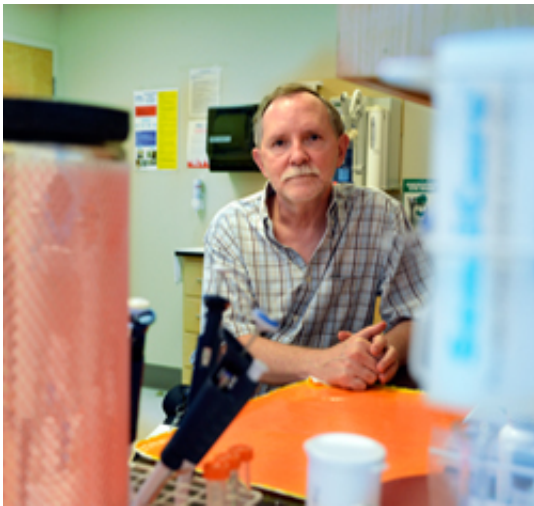


Researchers look for the best way to help shake too much sodium

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Dr. Gregory Harshfield is Principal Investigator on a \$10.6 million NIH grant looking at how stress, obesity, and inflammation conspire to produce impaired sodium excretion and increased blood pressure. Credit: Phil Jones, Senior Photographer, Georgia Regents University

Multiple times each day, about a third of blacks hold onto sodium – and higher blood pressure – for at least an hour after the stress that raised their pressure has passed, scientists say.

Now they want to know how chronic mental stress, obesity, and inflammation conspire to produce this unhealthy response so they can determine the best ways to treat it.

"We know that holding onto [sodium](#) is bad for you – these patients have increased damage to their hearts, their kidneys, and their vasculature – so how do we optimally treat them?" said Dr. Gregory Harshfield, Director of the Georgia Prevention Institute at the Medical College of Georgia at Georgia Regents University and Dorothy A. Hahn, MD Chair in Pediatrics.

Nearly a third of American adults – about 67 million people - are hypertensive and 35.8 million have uncontrolled hypertension, including 16 million individuals who are taking one or more medications, according to the Centers for Disease Control and Prevention.

Harshfield is Principal Investigator on a \$10.6 million Program Project grant re-renewal from the National Heart, Lung and Blood Institute that's enrolling 1,200 people in six different studies at MCG designed to parse the unfortunate synergy and test therapeutic strategies they hope will significantly reduce the uncontrolled number.

To better discern how all the multiple factors interact, parallel animal studies are being conducted by Drs. David and Jennifer Pollock, Director and Co-Director, respectively, of the Section of Translational Cardio-Renal Research at the University of Alabama at Birmingham School of Medicine.

Sodium retention, which is regulated by the kidneys, is a natural way the body responds to stress. It's part of the fight-or-flight survival mechanism that gets the heart pounding and the body moving quickly when needed, Harshfield said.

But he has shown that about 30 percent of blacks – and about 15 percent of whites - hold onto an additional 250 milligrams of salt – about what's found in a medium order of fast-food fries – each time they are stressed.

Now he and a team of researchers that also includes Dr. Ryan A. Harris, clinical exercise physiologist, and Dr. Yanbin Dong, geneticist and cardiologist, want to know exactly how that occurs. They suspect that it can vary with the individual. "We are trying to tease out the mechanism underlying sodium retention," Harshfield said.

It's a complex, interwoven chain of events that appears to start with stress activating the sympathetic nervous system in the kidneys, increasing the amount of sodium the kidneys retain rather than excrete. One way it does this is by activating angiotensin II, a powerful constrictor of [blood vessels](#) which, in turn, activates aldosterone, a hormone that prompts the kidneys to hold onto sodium. Angiotensin II also activates the immune system, which, interestingly, is directly activated by increased blood pressure and raises blood pressure.

Fat produces more of all of the above as well as [oxidative stress](#), which also damages blood vessels. Additionally, stress – as well as a high-salt diet – appears to decrease activity of the endothelin B receptor in the kidneys, which is also essential to sodium excretion, and increase activity of the endothelin A receptor, which prompts sodium retention.

Their bottom line is finding the most direct and effective place to interfere and help this group of individuals control their blood pressure, Harshfield said. "A lot of work in stress and hypertension has been done by psychologists and hasn't looked at hormonal factors underlying it. They have looked at the hemodynamics of blood pressure and heart rate, so we are trying to fill in those gaps of knowledge."

One irony they will further explore is that angiotensin receptor blockers, mostly considered ineffective in blacks, may work like a charm in blacks with impaired sodium retention.

"Angiotensin receptor blockers normalize sodium excretion and blood

pressure," Harshfield said of his team's experience with it to date. So they are using competitive video games to stress individuals who are high sodium retainers, giving one of these drugs, phentolamine, which dilates blood vessels and already is widely used for hypertension, heart failure, and to prevent kidney failure, then comparing the response to those who just get a placebo.

They are doing similar studies comparing the drug's effect on obese versus leaner sodium retainers, anticipating that it will be even more effective in obese individuals. To look at the impact of the immune system, they are comparing the effect of the immunosuppressant, mycophenolate, which transplant patients take, to placebo on sodium excretion, anticipating that while it may help, it won't be nearly as effective as the angiotensin receptor blockers.

To tease out the effects of endothelin, they will put study subjects' hands in ice water as a stressor then see whether a drug that inhibits the action of both the endothelin A and B receptors reduces their stress response.

A related focus is [early life](#) stress and free radicals, a natural byproduct of biological activity such as oxygen use that, at high levels, can wreak havoc in the body, including vascular dysfunction and even DNA damage. While clinical experience with antioxidants for cancer, as an example, has not panned out, Harris thinks the right combination of over-the-counter antioxidants in the right population may.

Rather than focusing on sodium retainers, he is looking at a cohort of individuals, now in their 30s, who were identified in childhood as being at high risk for hypertension and heart disease because of a strong family history. Some have the additional risk factor of early life stress, primarily from a low socioeconomic status. Harris will be using cold again to look at [stress response](#), anticipating those with early life stress will be the most responsive. He also anticipates that those individuals

will have the highest levels of oxidative stress – made worse if they are now also obese – and will benefit from a cocktail of over-the-counter antioxidants such as vitamins E and C and the cardioprotective alpha lipoic acid.

Pre- and post-therapeutic urine and blood samples from all study participants collected by Dong will give scientists a ton of human data, such as biomarkers that gauge immune system activity, which they can compare with animal data. The information may eventually lead to a physician being able to identify the specific reason their patient is retaining sodium.

Harshfield notes that once they find how best to treat sodium retainers, Identifying them – outside of a research setting – could be as simple as getting a second urine sample and [blood pressure](#) measure as patients head out of their doctor's office. Work by Harshfield and medical student Evan Mulloy indicates that the simple [stress](#) of a doctor's visit can help sort out the sodium retainers.

Dr. Varghese George, Chairman of the MCG Department of Biostatistics and Epidemiology, and a core leader on the grant, helped design the program project studies and will analyze collected data.

Provided by Medical College of Georgia

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