Female sex chromosomes, not just hormones, help regulate blood pressure

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Researchers at Georgetown University Medical Center (GUMC) have determined that something in female sex chromosomes appears to trigger a rise in blood pressure after the onset of menopause. This finding challenges the current belief that sex hormones are largely responsible for regulating blood pressure.

Their work, reported online Monday in Hypertension, is the first of its kind and involves male mice engineered to have female (XX) sex chromosomes, and female mice with male (XY) chromosomes. The findings suggest that sex chromosomes regulate blood pressure in and of themselves. Most researchers have thought that sex hormones (estrogen and testosterone) play key roles in controlling blood pressure and that women develop hypertension after reaching menopause because of loss of estrogen.

"Up until now, it has been impossible to separate the influence of sex chromosomes from the effects of sex hormones, and in this paper, we have shown for the first time that sex chromosomes are impacting blood pressure - independent of sex hormones," says the study's lead investigator, Kathryn Sandberg, PhD, director of the GUMC Center for the Study of Sex Differences in Health, Aging, and Disease.

"That is not to say sex hormones don't matter in blood pressure regulation, because they do, but we now know they aren't the only players," she says. "Estrogen likely works to protect against hypertension, but once the hormone is depleted, something is unmasked

on female XX chromosomes that allows blood pressure to rise."

Within their genome, men have two different sex chromosomes (an X from their mother and a Y from their father) while women have just one (two XX chromosomes, one from each parent). But only one gene - the all-powerful Sry gene - on the Y chromosome makes a man a male because it dictates development of male testes. Women arise when an Sry gene is absent resulting in the development of ovaries, Sandberg says. In utero, males and females are bathed in a soup of associated sex hormones, also dictated by presence or absence of the Sry gene, which leads to development of the male and female phenotype (hair, breasts, genitalia).

In this study, Sandberg and her team studied mice in which the Sry gene was deleted from the Y chromosome resulting in XY females. These mice were females because they were born with ovaries (which is what occurs when the Sry gene is missing) and exposed to estrogen in utero. They also studied XX males in which the Sry gene was put on one of the other 22 non sex chromosomes in the genome, which then dictated development of testes and testosterone. "The Sry gene just needs to be present in the genome. It does not have to be on the Y chromosome to create testes," Sandberg says.

The researchers could now make comparisons between the different mice. For example, the only difference, then between the XX and XY females, who developed in utero with the same hormonal environment, is the difference in the sex chromosomes. The same is true for XX and XY males. They could also compare the role that hormones played in blood pressure regulation between XX females and XX males, and XY females and XY males.

"Its a two-by-two analysis," Sandberg says. "If we find a difference between XX females vs. XY females that is also found in XX males vs.

XY-males then we can ascribe it to a sex chromosome effect and not a sex hormone effect."

And that is exactly what they did find in regard to blood pressure. "XX mice have a greater magnitude of hypertension than XY mice regardless of whether they are male or female," she says.

"That means there is something encoded in the sex chromosomes that is separate from hormonal influence that is impacting blood pressure in a significant manner," Sandberg says. "Researchers have found sex chromosome effects in some areas of brain and immune system function, but no one before has looked at this in the cardiovascular system."

Sandberg says there could be three explanations as to why this is occurring. One is a phenomenon known as "escape from X-inactivation." In each XX cell, only one X chromosome can be expressed, but it is known that some genes from the "silent" X chromosome escape this silencing. "These genes are known, and it is the same set of genes that escape X-inactivation, including in the XX males," Sandberg says. "We think there may be something special about these genes that escape X-inactivation and which are only expressed in XX cells."

The other possible explanation is conflict between cells that are expressing different parental X chromosomes. While each cell in a female expresses only one X, that X could come from either the male or female parent. Conflict can arise when a cell expressing a maternal X is adjacent to a cell expressing a paternal X. "That can drive an immune response because the two X's may recognize their own molecular self differently," she says.

The other theory is that the Y chromosome contains a gene or genes that protects against hypertension, and that "since postmenopausal women

don't have that added benefit from those Y genes, once the beneficial effects of estrogen are gone, blood pressure rises."

"These very exciting findings deserve much more research into what is encoded within the sex chromosomes that affects blood pressure control," Sandberg says.

She adds that if researchers can zero in on that particular mechanism, it may be possible to design a therapy to stop intransigent postmenopausal rise in blood pressure, Sandberg says. "There is a real jump in blood pressure and incidence of hypertension in menopausal women, and while the condition is treatable, blood pressure in many of these women is not fully under control making them far more susceptible to cardiovascular and kidney disease and stroke. Therefore, it would be wonderful to have specific therapies that target the root cause of this hypertension."

Provided by Georgetown University Medical Center

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