

## A peptide affects hypertension in mice

Essential hypertension — high blood pressure without any obvious cause — can affect as many as one person in five in the United States at some point during that individual's lifetime, the American Heart Association estimates.

Scientists know that both genetic and environmental factors, such as diet, play a role in the condition. But because many physiological systems influence blood pressure regulation, researchers have had a hard time teasing out the contributions of specific genes and their biological products.

One factor known to influence blood pressure is atrial natriuretic peptide (ANP). Produced naturally in the hearts of mammals, this 28-amino-acid molecule is stored in granules in the atria (upper chambers), then released into the blood. The peptide tends to cause blood vessels to dilate and the body to excrete salt.

Yet researchers have not yet determined whether or how genetic variations in ANP contribute to hypertension in humans.

Investigating this question, Simon W.M. John, a pathologist at the University of North Carolina (UNC) School of Medicine in Chapel Hill, and his colleagues report that, in mice, "genetically reduced production of ANP can lead to salt-sensitive hypertension."

In other words, mice genetically altered to have low amounts of ANP can become hypertensive when exposed to a high-salt diet; normal mice do not. The report appears in the Feb. 3 SCIENCE.

The researchers selectively disrupted the proANP gene — which regulates production of an ANP precursor molecule — in the test animals. Doing so reduced the animals' ANP by as much as half, says UNC pathologist Oliver Smithies, a coauthor. Mice with no ANP in their atria or circulating in their blood became hypertensive when fed a normal salt diet. Mice with some ANP in their blood maintained normal blood pressure.

However, when the researchers exposed mice with genetically lowered ANP to a high-salt diet, the animals grew hypertensive.

"We believe that many factors work together to cause essential hypertension in human beings," Smithies says. "We also think that humans are more likely to experience genetically determined variations in ANP levels, rather than its complete absence. For that reason, we thought it would be more relevant to human hypertension to look at decreases, rather than an absence, of ANP in mice."

"We find that when animals with decreased ANP levels are stressed with a high-salt diet, their blood pressure does rise," Smithies adds. "Normal wild-type mice can handle the increased salt. They just drink and pee a lot to excrete it. The only difference between these two types of mice is one altered gene."

Smithies believes this information will prove helpful in ferreting out the genetic factors in human essential hypertension.

"The beauty of this type of experiment is that genetically it's very clean," says Loren J. Field, a molecular biologist at Indiana University School of Medicine in Indianapolis. "You can make much stronger correlations between precise genetic alterations and blood pressure, which offers a significant advantage over standard animal models of hypertension."

"Clearly, this work shows that artificially induced genetic lesions in the ANP system can affect blood pressure in mammals," says Theodore W. Kurtz, a pathologist at the University of California, San Francisco. "That certainly suggests that such naturally occurring lesions may contribute to blood pressure regulation in human beings."

— R. Lipkin