Mutant rats offer clues to medical mystery

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A research project at Rice University has brought scientists to the brink of comprehending a long-standing medical mystery that may link cardiovascular disease, osteoporosis and perhaps even Alzheimer's disease.

And for that, we can thank the rat.

The recent paper in *Artery Research* by Rice evolutionary biologist Michael Kohn and his team reports they have found that common rats with a genetic mutation have developed a resistance to rat poison, aka warfarin. That's good news for the rats, but it comes at a price. The mutation also leaves them susceptible to arterial calcification and, potentially, osteoporosis.

The discovery is certainly good news for humans.

In the mutated gene, the researchers found what could be the link that solves the calcification paradox, the puzzling association between metabolic bone disease and vascular calcification that has eluded researchers for years. Kohn, an assistant professor of ecology and evolutionary biology, collaborated with Roger Price of the Baylor College of Medicine and Hans-Joachim Pelz of the Julius Kuehn Institute in Germany.

Kohn said a good part of the answer lies in the vitamin K cycle, which is known to regulate the coagulation of blood - clotting. It's also suspected of helping keep calcium out of the body's vessels and in its bones, which

has particular ramifications for postmenopausal women for whom loss of bone density is a nagging issue.

Warfarin has long served humans as a medicine called coumadin, because it interferes with the vitamin K cycle. In regulated doses, it thins the blood by reducing its ability to clot, helping prevent heart attacks, stroke and blood clots.

In bigger doses, it once excelled as rat poison; rats that ingested the poison would simply bleed to death. But a mutation in the gene Vkorc1 effectively blocks that interference.

"I have a feeling the mutation predated the introduction of warfarin," said Kohn. "But it was rare, because it causes side effects. It's not an advantageous mutation unless it's exposed to warfarin."

Poisoning rats without the mutation killed them, while those with the mutation multiplied. "And these rats, in the absence of poison, suffer from cardiovascular disease -- just like we do," said Kohn, adding that the kidneys of rats in the study were "calcified to an extent that is shocking."

His hope is that the equivalent gene in humans turns out to be the key to a number of ills.

"As you look at humans, this calcification of arteries is, I suspect, a very important precondition to thrombosis and stroke. So to find such a strong effect was shocking to us. We had a tough time publishing the paper because people might have thought it was too good to be true, that you can explain the effect to such a degree by looking at just one gene."

Kohn and his colleagues have begun a study on osteoporosis in rats that have the mutation, and early results are promising. "The prediction is the

mutant rats have a lower bone density. And I think if we complete and confirm that as well, it would be a major breakthrough. That means one gene, one mutation, explains the so-called calcification paradox."

Finally, he noted, Alzheimer's patients tend to be vitamin K-deficient, which opens up avenues for further study. "Could there be one mutation that explains osteoporosis, arteriosclerosis and Alzheimer's? That would be huge," said Kohn.

"I think the pathway of the vitamin K cycle is underrated in terms of its importance to some of these diseases. Gas6 is a vitamin K protein expressed in the brain, and there are many more vitamin K-dependent proteins we don't know about. The question is, if the recycling capability of the vitamin-K cycle is reduced, how many of these proteins can't do what they're supposed to do?

"I think we have some surprises in store."

Kohn said it's gratifying to know that evolutionary biology can help pave the path to personalized medicine. He credits the now-published findings with helping him land a recent grant of $900,000 from the National Institute of Heart Lung Blood disease at the National Institutes of Health. Kohn will now use mutant and normal rats to find additional genes that respond to warfarin, with two purposes: first, to see if rats have recruited additional genes to battle poisons that are more potent, and second, to attain the ultimate goal of fine-tuning doses of coumadin for humans.

More information: Kohn's paper is available here: www.arteryresearch.com/article … (08)00505-X/abstract

Source: Rice University