Gassing hypertension

By Brian Moy, Staff Writer

U.S. and Canadian researchers have shown that an endogenous gas, hydrogen sulfide (H_2S), can function as an endothelial cell-derived relaxing factor that regulates blood pressure.¹ The finding reveals potential new intervention points in hypertension, although open questions include which H_2S -synthesizing enzyme to target, how to specifically affect it and whether direct delivery of H_2S would be an option. In addition, balancing the potential toxicity of H_2S with its therapeutic benefits will remain a key challenge.

Under normal physiological conditions, H_2S is produced endogenously by two enzymes responsible for metabolizing L-cysteine: cystathionase (cystathionine γ -lyase) (CTH) and cystathionine β -synthase (CBS). In a paper in *Science*, researchers at Lakehead University, Johns Hopkins University and the University of Saskatchewan reported that *Cth* double knockout in mice led to an 80% decrease in endogenous H_2S levels in the aorta and heart compared with those seen in wild-type mice.

The knockouts also had more hypertension and less endothelium-dependent vasorelaxation than wild-type mice.

Furthermore, mice lacking both *Cth* alleles developed age-dependent hypertension beginning when the mice were seven weeks old. At 12 weeks, blood pressure in the mutant mice was almost 18 mmHg higher than that in wild-type mice.

“Our study is the first ever to show that removing H_2S by knocking out cystathionase in mice results in hypertension,” said Rui Wang, one of the principal investigators of the study and VP of research and a professor of biology at Lakehead University.

Gaseous translation

Although the *Science* paper implicates H_2S as a physiologic vasorelaxant, it's not yet clear how to translate the discovery into a therapeutic.

“From a practical standpoint, the *Science* paper identifies additional targets that could be used to treat hypertension as well as provides us with some insight into the physiologic mechanisms behind the disease,” said Carl Spana, president and CEO of Palatin Technologies Inc. “But while the paper shows how blocking cystathionase leads to hypertension, it does not provide a clear path forward for treating disease.”

Palatin's PL-3994, a subcutaneously delivered atrial natriuretic peptide receptor A (NPRA) agonist, is in Phase IIa testing to treat hypertension.

Solomon Snyder, a principal investigator of the study, agreed with Spana. “At this stage, our knowledge about the role of H_2S is very limited,” he noted. “While the study shows that H_2S is an important determinant in blood vessel relaxation and a major physiologic regulator of blood pressure, we don't exactly know how to translate our findings into a therapy for hypertension.” Snyder is professor of neuroscience at Johns Hopkins University School of Medicine.

Spana thinks small molecules that enhance the production of H_2S could be a potential strategy for upregulating CTH.

Wang suggested that “administering exogenous H_2S by means of an H_2S -releasing compound or H_2S inhalation could someday prove to be applicable for treating hypertension if we are able to tightly control the dosage and duration of response.”

David Lefer, a professor in the Division of Cardiothoracic Surgery at Emory University School of Medicine, said, “The main question will be whether or not enhancing H_2S formation can promote a sustained reduction in blood pressure that is therapeutically equal to or better than currently marketed products to treat hypertension.”

One concern, said Lefer, is that “most investigational compounds available to deliver H_2S have an extremely short half-life and would therefore probably only lower blood pressure temporarily. We would need to identify drugs with a longer duration of action that can increase H_2S and ultimately lower blood pressure for a sustained period of time.”

He said further studies also will need to investigate the safety of any H_2S therapeutics. Toxic effects of inhaled H_2S include olfactory epithelial toxicity, a transient loss of olfaction and pulmonary inflammation and toxicity.²

To turn the H_2S findings to practical use, said Wang, “we need to be aware of the fact that in some organs, modulating levels of H_2S may not be beneficial, such as in the pancreas where increased levels of H_2S in pancreatic β -cells inhibits insulin release and leads to diabetes. It will be important to specifically target the organs in which an increase in H_2S is desired.”

Ongoing studies by Wang and colleagues are continuing to validate the role of H_2S as an endothelial cell-derived relaxing factor as well as investigating other diseases in which enhancing levels of H_2S may serve a therapeutic purpose.

Snyder is currently comparing the relative contributions of nitric oxide (NO) and H_2S to blood vessel relaxation.

Wang told SciBX the findings from the *Science* paper are neither patented nor licensed.

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