A vitamin B12 derivative could potentially be used to treat hypertension and heart disease

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Investigators at the University of California, San Diego School of Medicine have developed a new drug called nitrosyl-cobinamide. Cobinamide is a vitamin B12 analog, and, in fact, is the penultimate compound in the biosynthesis of vitamin B12 by bacteria. The UCSD investigators have shown that cobinamide binds relatively tightly to nitric oxide (NO), forming nitrosyl-cobinamide.

Because the binding is reversible, nitrosyl-cobinamide can be used as a NO donor. NO is produced by most cells in the body, and helps regulate a variety of physiological functions including maintaining blood pressure, optimizing heart function, and serving as a neurotransmitter. The report on this study, led by Dr. Gerry R. Boss, will appear in the December 07 issue of *Experimental Biology and Medicine*.

Two NO donor drugs have been in clinical use for many years: nitroglycerin (and its derivatives), and sodium nitroprusside. Nitroglycerin is used to treat angina because it increases blood flow to the heart by dilating the coronary arteries and reduces the work load of the heart by reducing venous return to the heart (preload) and by reducing blood pressure (afterload). Sodium nitroprusside is used to treat acute hypertensive episodes because of its potent blood pressure lowering properties.

Unfortunately, neither agent is ideal. Nitroglycerin is an organic nitrate and requires biotransformation in the body; tolerance develops rapidly, in large part due to the biotransformation process. Nitroprusside releases

five cyanide ions for every NO molecule released, and, therefore, drug treatment is limited by cyanide toxicity. A clear need exists for a non-toxic direct NO donor.

Nitrosyl-cobinamide may be such an agent, because Dr. Gerry R. Boss, Professor of Medicine at UCSD, and his colleagues showed that nitrosyl-cobinamide was active as an NO donor in several different biological systems: cultured rat pulmonary artery smooth muscle cells, Drosophila Malpighian tubules, isolated mouse hearts and aortas, and whole animal mouse studies. In the isolated mouse hearts and the whole animal studies, the UCSD team showed that nitrosyl-cobinamide was more effective than nitroglycerin in increasing coronary blood flow and lowering blood pressure, respectively.

Nitrosyl-cobinamide is a direct NO donor and does not require biotransformation. As a vitamin B12 analog, the parent compound cobinamide appears to be non-toxic at the doses that would be required to treat angina or acute hypertension; formal toxicology and pre-clinical pharmacokinetic studies of cobinamide are currently underway.

Source: Society for Experimental Biology and Medicine