

Nitric oxide and its role in health and diabetes.

Thomas Burke Ph.D.

Part 4. How Nitric Oxide (NO) causes vasodilation.

NO initiates and maintains vasodilation through a cascade of biological events that culminate in the relaxation of smooth muscle cells that line arteries, veins, lymphatics. While somewhat complex, the sequence of biological events that are triggered by NO is described below:

Step 1. NO gas released from nitrosothiols in hemoglobin or from endothelial cells, diffuses into smooth muscle cells that line small blood vessels.

Step 2. Once inside the smooth muscle cell, NO binds to an enzyme, called guanylate cyclase (GC) and this binding results in GC activation.

Step 3. Activated GC is able to cleave two phosphate groups from another compound called guanosine triphosphate (GTP). This results in the formation of cyclic guanosine monophosphate (cGMP) that is used to phosphorylate (Phosphorylation is the addition of a phosphate group) proteins, including the smooth muscle contractile protein called myosin.

Step 4. Once phosphorylated, smooth muscle cell myosin relaxes, resulting in dilation of the vessel that was originally exposed to NO.

As one can imagine, only a limited number of GC enzymes are present in any one smooth muscle cell and once all the GC enzymes have been activated, additional NO will not initiate any further vasodilation. Any “extra” NO is simply sequestered as a nitrosothiol bound to hemoglobin in RBC for future use.

Eventually the phosphate groups bound to myosin in smooth muscle cells must be removed to return the blood vessels to their normal diameter. This removal, or de-phosphorylation, is accomplished by another enzyme, a phosphatase. If the phosphatase enzyme is inhibited, then NO/GC/cGMP mediated vasodilation will be sustained for a longer period of time. This, in fact, is the basis of the erectile dysfunction drug Viagra™; which inactivates the phosphatase.

What does this mean for people with diabetes and for their physicians? Clearly, normal vasodilation cannot occur in patients whose NO production or release is depressed, as we

pointed out in previous articles. Without vasodilation, healing of ulcers will be slow, development of nerve damage will accelerate, and circulation to organs such as eyes, kidney, heart, and intestine will remain below normal.

Some may ask whether it isn't "too much" vasoconstriction rather than "too little" vasodilation that characterizes poor perfusion in people with diabetes? In normal subjects, the control of perfusion involves several vasoconstrictor hormones and activation of sympathetic nerves, which together cause vasoconstriction. To induce vasodilation, the body must reduce these biologic responses or counter them with vasodilators such as NO (or a prostaglandin called prostacyclin). Therefore, in the absence of normal concentrations of NO, even normal levels of vasoconstrictive hormones or nervous activity results in abnormally low blood flow (vasoconstriction and its effect to reduce tissue perfusion). One does not need to implicate "too much" vasoconstrictive activity (via hormones or nerves) as a cause of perfusion problems in people with diabetes, although this certainly can be a contributing factor in some instances.

In summary, NO causes vasodilation by initiating a cascade of biological events that relax smooth muscle cells lining blood vessels. This vasodilation continues until a phosphatase enzyme dissociates the phosphate from myosin (which may be delayed by Viagra). Since vasodilation through NO only occurs when there is GC able to bind NO, additional NO, is sequestered for future use as a nitrosothiol, including those found in hemoglobin. NO is the most important of the body's countermeasures against normal vasoconstriction and, if production or release of NO is impaired, as in the case of people with diabetes, poor circulation, and all the consequences thereof, ensues.

Many people with diabetes exhibit loss of sensation, a phenomena that is linked directly to an abnormality in nerve function. The loss of nerve structure and function has been attributed to a decreased circulation induced, in part, by decreased production of NO. The relationship between NO, vasodilation, blood flow, and nerve function will be discussed in the next article.

Dr. Tom Burke received his PhD in Physiology from University of Houston, Post Doctoral Training at Duke Medical School, He was an Associate Professor of Medicine and Physiology at the University of Colorado Medical School. He has authored more than 70 published scientific clinical articles and has been a visiting scientist at the Mayo Clinic, Yale University, University of Alabama, and University of Florida. He is a recognized international lecturer on cell injury and nephrology.