Part 1. Discovery of NO, Nobel Prize, relevance in vasodilation

This is the first in a series of articles that relate specifically to nitric oxide (NO), a free radical gas that is a powerful regulator of circulation (it is an endogenous vasodilator) and a neurotransmitter (it helps in the processing of nerve signals as they cross synapses). L-arginine, one of 20 amino acids that make up proteins, is the only amino acid that generates significant amounts of NO. Both circulation and neural function are impaired in diabetic patients, more so if tight glucose control is not maintained.

The Nobel Prize was awarded to three Americans in 1998 for their work on discovering NO and clarifying its role in health. Their most important contributions lay in describing the effect of NO on the circulation that, as everyone knows, is disturbed to one degree or another in diabetic patients. The question then becomes is NO metabolism or action deranged in diabetic patients and could NO have a role in preventing some of the consequences in diabetes? We certainly believe so and will develop this theme in this and succeeding articles.

The blood flow and nerve responses are rapid. Small increases in NO lead to both vasodilation and to better sensory perception. We will discuss the enzymes that generate NO in later articles in this series. Suffice it to say that NO metabolism is necessary for normal circulation (venous, arterial, and lymph flows) and for the ability to sense pain, temperature, and pressure. Diabetic patients have deficits in circulation, which often lead to blindness, kidney dysfunction, heart disease, and ulcers in the lower legs. Clearly circulation is impaired in diabetic patients. In addition, peripheral neuropathy (the inability to sense pressure or temperature in the feet) is a consequence of diabetes in many patients. Diabetic peripheral neuropathy (DPN) is a primary cause of ulcers and eventual amputation of digits or even whole limbs.

Is there evidence that NO metabolism is impaired in diabetic patients? The answer is yes and that too will be discussed in a later article.

L-arginine, the source of NO is released from proteins and small peptides in the small intestine and is then absorbed, along with other amino acids into the circulation from which it is delivered to every cell in the body. Some L-arginine is metabolized for NO synthesis and some is used for protein synthesis. In endothelial cells, the small cells that make up capillaries and line every blood vessel and lymph duct in the body, L-arginine can be converted to NO. This occurs only if the enzyme that makes NO and it's co-factors are available in adequate amounts. In diabetic patients, athrsoclerotic disease often occludes a portion of a vessel so that the endothelial cells are not able to properly absorb NO. If the endothelial cell can't take up L-arginine, then NO synthesis will be impaired. Moreover, if athrosclerotic disease is present, oxygen delivery to all cells is impaired and molecular oxygen is one of the cofactors needed by the enzyme to generate NO from L-arginine. The NO diffuses into the smooth muscle cells that surround the endothelial lining of blood vessels cells causing a biologic chain of events that lead to

smooth muscle cell relaxation. This results in more blood flow to the tissues. Tissues that are hypoxic (deprived of good, normal circulation) can not produce as much NO as do normal, well oxygenated tissues. Thus an initial period of hypoxia leads to declines in NO production and less and less blood flow over time, a viscous cycle to say the least. It is no wonder that diabetes is a progressive disease with wounds, kidney, heart, and eye disease becoming worse and worse over time.

The next article in this series will examine the enzyme that generates NO from L-arginine. This is an important topic since there are three forms of the enzyme and each exerts slightly different effects on the amounts and timing of NO production.

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