

Nitric oxide and its role in health and diabetes.

Thomas Burke Ph.D.

Part 7. Nitric Oxide (NO) and Relief of Pain.

NO offers pain relief in a number of ways. In fact, NO is the mediator of the analgesic effect of opioids such as morphine. In this article we describe how NO affects pain responses and, in particular, certain pain responses in people with diabetes.

Nerves can only function if they are structurally intact. Nerves must have a normal membrane potential maintained by ion (potassium and sodium) pumps that derive energy from the synthesis of ATP. However, compromised circulation, which is often the case in people with diabetes, causes nerves to malfunction, due in part to the absence of normal amounts of oxygen and nutrients (such as glucose), which together synthesize ATP. Lack of adequate oxygen and nutrients, and the lower synthesis of ATP, adversely affects normal membrane potential. Under normal conditions, nerves operate at -70 mV (millivolts) and fire (signaling pain) at -20 mV. Due to lack oxygen and nutrients, the membrane potential more closely approximates -20 mV and in those circumstances it takes little stimuli to reach the firing threshold. Poor circulation to the nerves prevents them from sending the appropriate signals (for pressure and temperature) to the brain and often the poor circulation is first perceived as pain. NO mediated vasodilation will increase delivery of oxygen and nutrients to poorly perfused nerves to re-establish their normal membrane potential. Patients with diabetes are often given strong painkillers in an attempt to modulate the pain. These drugs do nothing to restore normal nerve function.

Reduced perfusion as a result of acute injury or chronic circulatory disorders causes swelling or edema, and this added fluid accumulation exerts pressure on the nerves, which can cause pain. Swelling also compresses capillaries that provide oxygen to the nerves (and other tissues as well). Consider the pain that occurs when, as a child, you put a rubber band around your finger. The finger turned blue, it swelled, and it eventually became so painful that you had to remove the rubber band. NO, which increases arterial flow to nerves and venous drainage away from nerves, counters the "rubber band" like effect of impaired diabetic circulation and in doing so removes the edema and swelling.

Medical researchers have often missed the significance of research conducted nearly a decade ago. NO was shown in the early 1990's to be the mediator of the analgesic effect of opioids such as morphine (SH Ferreira, 1991). Other studies, by this same group, showed that this beneficial effect was due, in part, to a morphine-mediated increase in NO and then in cGMP. Thus, it now appears that morphine binds to a nerve cell receptor, initiates a release of NO and there is a subsequent diminution in pain, mediated by cGMP. Therefore, raising local levels of NO can mitigate pain.

In understanding the ways that NO can reduce pain, it is easy to realize its significance in people with diabetes. Impaired circulation is a typical consequence of this disease. Disturbed membrane potential would be anticipated thus decreasing the stimuli necessary for nerve firing and perception of pain. Additionally, this impaired circulation often leads to swelling in the extremities, exerting pressure on the nerves, which also causes pain. Lastly, diffuse extremity pain is often associated with peripheral neuropathy. NO mediated increases in cGMP may directly reduce this neuropathic pain.

In summary, NO may reduce pain associated with diabetes directly by increasing cGMP (the mechanism by which opioids work), and indirectly by increasing circulation to restore normal membrane potential and reduce pressure on nerves due to localized edema.

The next article will discuss diabetic peripheral neuropathy (DPN), the leading cause of ulcers and amputations among people with diabetes. This is especially timely because on October 17, 2001, CMS published a Decision Memorandum recognizing DPN with loss of protective sensation as a localized illness of the feet.

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.