

Nitric oxide and its role in health and diabetes.

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Part 5. NO and neurotransmission.

Diabetic patients are particularly at risk for damage to sensory and motor nerves in the feet or to dysfunction of the autonomic nervous system that innervates internal organs, for example, the intestine. The clinical diagnosis of the latter condition is gastroparesis. NO is an important signaling molecule conveying information from one nerve to another, including non-cholinergic, non-adrenergic (NCNA) nerves. NCNA nerves control smooth muscle cells, which regulate gastric emptying and intestinal motility. Reduced availability of NO in diabetic patients may be one cause of gastroparesis.

Nerves communicate with one another across synapses and several biochemical compounds diffuse from one nerve to the second nerve. NO is one of these biochemical “neurotransmitter” molecules and is produced by both brain tissue and peripheral nerves.

NO has both a direct and indirect effect on neurotransmission. The direct effect relates to permeability of nerve membranes regulating ion transport that is important for nerve signal transmission. Indirectly, NO enables nerves to properly function by causing increases in blood flow (vasodilation) allowing essential oxygen and nutrients to be transported to nerve cells.

Direct: Dispersal of ions across the nerve cell membrane is dependent, in part, on transporter proteins that act as channels for ion transport. These channels regulate the permeability of the cell membrane. As was the case for the smooth muscle cell protein myosin, the contractile protein described in part 4, phosphorylation of these channels is essential in controlling ion permeability of the membrane of the nerve. Physiologic changes in ion permeability determine the transmission of impulse along the nerve. In nerve cells, NO generates cGMP (as described in Part 4), which results in phosphorylation of a nerve cell ion channel that is permeable to potassium ions. Thus, NO must be present in order to regulate membrane permeability to potassium ions, which is necessary for nerve signal transmission. Normalization of the inadequate NO levels in diabetic patients can directly impact nerve function by improving nerve membrane permeability to potassium ions.

Indirect: Poor circulation to feet and the lower leg, possibly a result of impaired NO-mediated vasodilation, results in swelling (edema), tissue damage, and ulcers. The lack of oxygen and nutrients also adversely affects nerves that also rely on oxygen and glucose to generate the energy source, adenosine triphosphate (ATP). ATP maintains ions such as potassium and sodium at normal physiologic concentrations inside and outside nerve

cells. If oxygen and glucose delivery to nerves is impaired, then normal levels of ATP will not be generated. This event adversely affects potassium/sodium homeostasis across the membrane. The nerves will not receive and process information (touch, temperature) when the potassium and sodium ions become chronically disturbed due to the lack of sufficient oxygen and nutrients. In addition, bNOS found in some peripheral nerves is, like ecNOS, is an oxygen dependent enzyme. The lack of oxygen available to the nerve itself would impair formation of NO and compromise neurotransmission. Nerves, like other tissues are supplied with oxygen through blood vessels. By inducing vasodilation and improving circulation, NO can improve nerve function by increasing available oxygen and glucose, thereby allowing ATP production to establish normal ion concentrations across the nerve cell membrane. Specifically, increased oxygen availability to the bNOS enzyme will improve impaired formation of neural NO and thus neurotransmission.

In summary, NO has both a direct and indirect influence on neurotransmission. NO, by affecting cGMP, allows phosphorylation of ion channels, especially potassium channels necessary for normal transmission of nerve signals. NO also increases blood flow. This allows sufficient oxygen and glucose to be transported to nerve cells, positively affecting ATP production and, in turn, potassium/sodium homeostasis essential for neurotransmission. Increases in blood flow may also allow the oxygen dependent isoform, bNOS, to produce more NO.

NO is also a powerful regulator of cell division and proliferation necessary for tissue repair. In the next article, we will discuss the involvement of NO in tissue repair and wound healing, including the regeneration of nerves.

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