

Nitric Oxide in Biology: Making it and Using it – Neither is Easy

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Since the discovery of nitric oxide (NO) formation in animals, it has become clear that this toxic, free radical, diatomic gas plays a central role in cellular function in eukaryotes. NO acts as a cell-to-cell signaling agent in the cardiovascular system and the central nervous system. The immune system uses NO in the host response to infection. NO used in signaling is synthesized by the constitutive isoforms of enzyme nitric oxide synthase (NOS) that are tightly regulated by Ca^{2+} and calmodulin, leading to nM levels of NO. The inducible isoform of NOS synthesizes NO unregulated leading to μM concentrations in a localized site of infection. NOS catalyzes the conversion of arginine to citrulline and NO. This complicated reaction is carried out by an equally complicated protein. Using a low concentration of NO in signaling solves the toxicity problem but places a difficult chemical requirement on the NO receptor, the soluble isoform of guanylate cyclase (sGC). sGC contains a heme cofactor that acts to trap NO, thereby activating the enzyme to convert GTP to cGMP. The heme domain of sGC was found to be part of the H-NOX (Heme-Nitric oxide OXYgen) family of proteins with homologues in aerobic and anaerobic prokaryotes. Structural and biochemical studies have provided a molecular explanation for selective NO trapping at low concentrations. NOS-like proteins have been found in prokaryotes, as have proteins that could function as selective NO receptors. Clearly the function of NO in biology is even more pervasive and more complicated than originally described. The structure/function picture that is emerging points to some common themes though many questions remain.