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BAKER APPLICATION BULLETIN

Why is Oxygen level linked to everything Nitric Oxide does?

Oxygen; nitric oxide; hypoxia; angiogenesis; immune response; synaptic communication; cancer

TOPIC

Nitric oxide (NO) is a crucial signaling molecule in diverse biological processes. Dysregulation in NO signaling or its bioavailability is involved in various disorders. It is also sensitive to oxygen concentrations as Oxygen (O_2) is a major determinant of synthesis and metabolism.

BACKGROUND

In the research setting, real biology can only be, for obvious reasons, mimicked. When researchers want to understand phenomena occurring in a cell, for example, its functions need to be ripped apart to a few isolated events in order to be studied. Only from understanding these basic components of the cell can researchers then add additional layers that affect cellular life, finally and hopefully resulting in a comprehensive picture of the entity.

Throughout this process of learning, utmost attention needs to be paid to the environment the cell faces while undergoing the experimental procedures. If the experimental environment is wrong, the fundamental results derived from the experiments may prove to be profoundly misleading.
One of the most important, and often overlooked, environmental factors is Oxygen (O_2). Although it's approximately 21% of the atmosphere at sea level, it is never found in such quantities in tissues. In fact, oxygen forms gradients within tissues which are dependent on the rates of delivery from the vasculature and mitochondrial consumption. In plants, steep oxygen gradients can occur as they lack an active transport mechanism of O_2.

Nitric oxide (NO) is a signaling molecule that will act on a variety of targets within the cell. NO regulates vascular tone and blood flow throughout the body and has a role in protein methylation in response to environmental alterations (Frungill L et al., Thomas DD et al.). Abnormalities in vascular NO production and transport have been implicated in cardiovascular pathologies, and in the brain, NO regulates basic physiological processes that affect cognitive function. NO bioavailability has also been implicated in cancer development and changes to its synthesis, release or signalling have been shown to contribute to the pathogenesis of pulmonar arterial hypertension (PAH; Chester Ah et al).

Throughout the widespread functions of NO signaling, the fundamental step is its production. Cells have two different ways of producing NO, the L-arginine dependent and the nitrite-dependent pathway (Keshet R et al.). Importantly, both are regulated by oxygen concentration as a rate-determining step. The arginine pathway functions optimally in higher O_2 levels and is oxidative, the O_2- -dependent pathway favours lower O_2 and is reductive (Figure 1). O_2 acts as a substrate for nitric oxide synthase and thus determines NO metabolism rate. Therefore, local O_2 concentration has to be factored in

BACKGROUND CONT'

when determining the steady-state NO concentration, as the cellular milieu will also govern the duration of the NO exposure. This is critical because longer NO exposure has been linked to prolonged cancer cell survival whereas shorter NO exposure leads to enhanced apoptotic activity, cell cycle arrest and senescence. In addition, oxygen doesn't only regulate NO production, NO itself has a feedback loop -through a type of oxygen-dependent signaling via HIF-1. NO modulates the HIF-1 response under hypoxia and it also functions as a HIF-1 inducer in a concentration- and time -dependent manner (Sandau KB et al.)

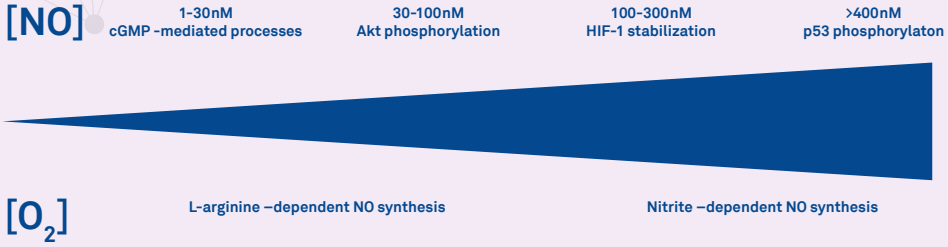

Figure 1. Concentration dependent processes of NO and O_2

WHAT TO LOOK FOR?

O_2-regulated nitric oxide is a free radical that has effects in almost all cellular signaling event from plants to humans:

- angiogenesis
- smooth muscle tone and reactivity
- immune response
- apoptosis
- synaptic communication
- protein methylation
- cancer metastasis
- cell differentiation
- plant cell lignification
- root and shoot development
- flowering
- growth and reorientation of pollen tubes
- plant-pathogen interactions

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