Nitric Oxide 85 (2019) 53

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

# Editorial for special issue: "Pharmacology & medicinal chemistry of nitric oxide"

**Preface**: Since its discovery ~30 years ago, nitric oxide (NO) has emerged as a fundamental regulator of a diverse range of essential biological processes. Endogenous synthesis of NO by nitric oxide synthases (NOS) can be highly regulated to elicit specific localized transient and/or sustained biological effects based on the distinctive diffusion properties and unique chemical reactivity of NO. NO is relatively lipophilic, and, in contrast to most biomolecules, NO is paramagnetic (i.e., it possesses an unpaired electron). Since reactions between paramagnetic and diamagnetic species are limited by spin forbiddenness, NO freely traverses membranes and diffuses readily thru biological environments until reacting with other paramagnetic species, usually molecular oxygen ($O_2$). In essence, although NO is a radical, it is remarkably unreactive and possesses a fair degree of selectivity with regards to the species with which it will react. Despite discretional reactivity, NO possesses a relatively short half-life (a few seconds) due to the high levels of $O_2$ and reactivity toward related species, including superoxide anions [$O_2^{\cdot-}$]; metalloenzymes (e.g., soluble guanylyl cyclase [sGC], hemoglobin, etc.); nitrogen dioxide ($NO_2$); and hydroxyl radicals ($^{\cdot}OH$). Measuring NO directly is logistically challenging and its short biological half-life creates an additional hurdle for therapeutic development, necessitating an unconventional approach to NO drug discovery.

Disease pathology is often multifactorial in nature and a multifaceted approach may provide the best therapeutic option. Direct alteration of NO concentrations, using either exogenous delivery from NO donors (i.e., agents which produce molecular $NO^{\cdot}$) and NO mimetics (i.e., agents which elicit effects seen with NO via an undefined/uncharacterized nitrogen oxide specie ($NO_x$), such as $NO^{\cdot}$; HNO; $NO^+$; $N_2O_3$; $NO_2^-$; ect.) to increase NO or nitric oxide synthase (NOS) inhibitors to decrease NO, could provide a therapeutic approach that combats multiple pathologic mechanisms. NO produces a variety of effects in addition to activation of canonical NO/sGC/cGMP signaling. These effects include: 1) nitrosylation of metalloenzymes (in addition to sGC); 2) the regulatory effects associated with post-translational modification (e.g., S-nitrosothiols, 3-nitrotyrosine, 8-nitroguanine, etc.); 3) free radical scavenging (e.g., termination of lipid peroxidation and detoxification of reactive oxygen species); and 4) compensatory changes in NOS expression and related stress response mechanisms. Clearly, directly modulating NO results in exceedingly complex biological consequences.

The most robust biological effect of NO is activation of the second messenger sGC which results in amplified production of cyclic guanosine monophosphate (cGMP, a potent vasodilator) and activation of an array of intracellular kinase signaling cascades, including pathways modulated thru protein kinase A (PKA), protein kinase B (commonly referred to as Akt) and protein kinase G (PKG). Several attempts have been made to mimic the biological effects of NO via modulation of these downstream kinases, as described in one article in this issue detailing pharmacological manipulation of cGMP signaling. In theory, an advantage of this approach is that it should be much simpler than targeting NO directly. These type of agents (e.g., sGC activators or phosphodiesterase inhibitors [PDEi]) are more amenable to traditional drug discovery approaches because they do not involve prodrug activation or the complex cellular responses to NO itself. Furthermore, tissue specific expression of PDE isoforms makes it possible to localize effects to a particular target tissue, a benefit not currently available for NO donors/mimetics.

In order to harness NO in novel therapies we must consider important properties associated with the druggability of these agents. Principal amongst these properties are ADME (absorption, distribution, metabolism, and excretion) characteristics, which inform dosing required for target exposure and prediction of pharmacodynamic response. A central challenge associated with NO drug discovery is how to appropriately define ADME characteristic, since NO mimetics are technically a prodrugs which are activated to a biologically active metabolite, $NO_x$. The chemical instability of most NO mimetic drug classes makes it difficult to measure prodrug absorption and distribution and measuring the specie responsible for biological effects, NO, is logistically cumbersome. The articles within this special issue are designed to shed light on the advancements, challenges, and limitations of our contemporary understanding of NO pharmacology and medicinal chemistry. This includes accounts of research employing novel basic science paradigms and considerations of pharmacokinetics, pharmacodynamics, and pharmacology of agents targeted at NO signaling.

https://doi.org/10.1016/j.niox.2019.01.010

Available online 16 January 2019