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Nitric Oxide Regulation of Penile Erection: Biology and Therapeutic Implications

ARTHUR L. BURNETT

From the Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland.

Correspondence to: Dr Arthur L. Burnett, Department of Urology, Marburg 407, Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21287 (e-mail: aburnett {at}jhmi.edu).

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For approximately a decade now, substantial evidence has accrued supporting nitric oxide (NO) as the central component of a major signal transduction system that acts in the penis to mediate the erectile response. This molecule subserves a unique biochemical cascade involving production of the potent second-messenger molecule, 3', 5'-cyclic guanosine monophosphate (cGMP), and its activation of protein kinase G (PKG), which induces physiologic penile erection by regulating the state of penile smooth muscle contractility (Burnett, 1997). In fact, current data support the notion that this NO-based biochemical cascade represents a convergence of cellular, biochemical, and molecular inputs, which, on the signal transduction regulatory level, is indispensable for the mechanism of penile erection (Hedlund et al, 2000a). Consistent with the importance of NO mediation of penile erection, its biology in the penis is quite complex, involving multiple regulatory interactions: the molecule itself may target several biochemical mechanisms that achieve erectile tissue relaxation, but it is also the target of a host of modulatory influences that determine its release and mode of action in erectile tissue.

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Precepts of an integrated nitric oxide-dependent regulatory system for penile erection

At the same time, this premier signal transduction mechanism has been exploited for therapeutic purposes, specifically in the clinical management of erectile dysfunction. Discoveries pertaining to the field of NO biology in the penis have, in recent years, been rapidly translated into the clinical development of the first orally effective pharmacotherapy for erectile dysfunction, sildenafil citrate (Viagra) (Goldstein et al, 1998). This medication and other similarly acting agents, either currently awaiting governmental regulatory agency approval for clinical distribution or undergoing scientific investigation (Noto et al, 2000; Oh et al, 2000; Hosogai et al, 2001; Padma-Nathan et al, 2001; Porst et al, 2001), describe a class of phosphodiesterase-5 (PDE-5)

inhibitors that uniquely interact with the biochemical processing of NO to boost the erectile signal (Boolell et al, 1996; Turko et al, 1999). It is apparent that various mechanistic opportunities related to NO signaling and processing in erectile tissue will be promoted as eventual pharmacotherapeutic strategies in the treatment of erectile dysfunction. Such expectations for promising treatment modalities based on the science of NO in the penis would imply continued optimism for the future management of erectile dysfunction.

NO-Dependent Signal Transduction

While NO may operate in several ways to direct the relaxation of corporal smooth muscle in the penis, it is best characterized as initiating a prominent biochemical mechanism of action for penile erection. Its key role involves signal transduction (defined as the intracellular or transcellular delivery mechanism in which an initially released chemical signal is transmitted and amplified by a second-messenger molecule) (Figure 1). According to this mechanism, NO is constitutively produced and released from autonomic nerve terminals and endothelial cells in the corporal tissue, diffuses locally into adjacent smooth muscle cells, and binds with intracellular guanylate cyclase, which serves as a physiologic "receptor" for the molecule (Burnett, 1995, 1997). This binding induces a conformational change of guanylate cyclase, activating the enzyme so that it catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. cGMP then operates through a cGMP-dependent protein kinase to regulate the contractile state of the corporal smooth muscle (Hedlund et al, 2000a). Among possible mechanisms for the downstream activities of cGMP, this molecule may direct phosphorylation changes of myosin light chain cross-bridging, control calcium and potassium ion fluxes and stores, interact with other signal transduction mechanisms, and otherwise exert effects on cellular contractile proteins independent of phosphorylation biochemistry (Burnett, 1995; Chuang et al, 1998). Recent experimental studies further suggest that cGMP inhibits the presynaptic release and contractile effects of the adrenergic contractile neurotransmitter, norepinephrine (Minhas et al, 2000).

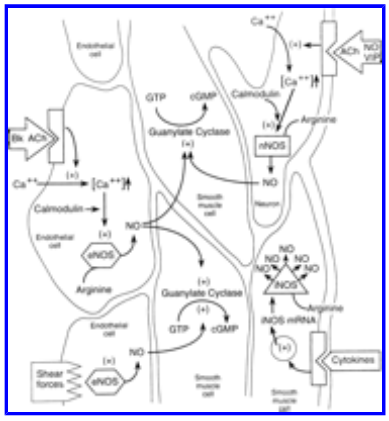

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Figure 1. Diagrammatic representation of nitric oxide (NO) synthesis, regulation, and action in the penis. Constitutive formation of NO derives from its precursor, L-arginine, under the catalytic action of the NO synthase (NOS) isoforms nNOS and eNOS, respectively, on the basis of the cellular localizations of the enzyme to neurons and endothelial cells. Conventional signal transduction involving NO constitutively is characterized by messenger molecules that commonly activate NOS isoforms by signaling influx of calcium and its binding with calmodulin. Other biochemical and mechanical factors may also interact with this process, stimulating the production of NO. Once synthesized, NO diffuses to local smooth muscle cells, where it primarily activates soluble guanylate cyclase to convert 5'-guanosine triphosphate (GTP) to 3', 5'-cyclic guanosine monophosphate (cGMP). Smooth muscle cells represent another source of NO, but they appear to require cytokine stimulation of inducible NOS (iNOS) expression. Bk indicates bradykinin; Ach, acetylcholine; and VIP, vasoactive intestinal peptide. (Reprinted with permission from Burnett, 1997.)

NO-associated relaxatory effects in corporal smooth muscle, independent of cGMP action, have also been described. This agent stimulates Na^+/K^+-ATP, resulting in direct hyperpolarization of the corporal smooth muscle cell, which prevents the opening of voltage-dependent calcium channels and thereby attenuates tissue contraction (Gupta et al, 1995). NO may also influence a potassium conductance pathway within corporal smooth muscle cells, resulting in hyperpolarization (Seftel et

al, 1996; Lee and Kang, 2001).

NO Biology in the Penis

Classic Concepts— Traditional understanding of the action of NO in the penis invokes the constitutive formation of this molecule under normal physiologic conditions with the expression and activities of the enzyme sources localized to neural and endothelial components of the corporal tissue. The verification that NO derives from the autonomic innervation supplying the penis has directly supported the description of this molecule as a peripheral neurotransmitter of nonadrenergic, noncholinergic-mediated penile erection (Kim et al, 1991; Burnett et al, 1992; Rajfer et al, 1992). The confirmation that the molecule also is produced within the vascular and trabecular endothelium comprising the penile vascular supply has offered additional support for the role of NO serving as an endothelial relaxation factor of penile erection (Kimoto et al, 1990; Knispel et al, 1991; Azadzoi et al, 1992; Hedlund et al, 2000b).

The catalytic production of NO requires NO synthase (NOS), expressed in many biological tissues as 3 main isoforms: neuronal NOS (nNOS or NOS I), inducible NOS (iNOS or NOS II), and endothelial NOS (eNOS or NOS III) (Forstermann et al, 1998). Both nNOS and eNOS, which do pertain to the original cellular sites of their identifications, are constitutive isoforms requiring calcium-binding protein calmodulin, oxygen, and reduced NADPH for catalytic activity. These isoforms generate NO transiently and in low amounts, appropriate for cell-cell signaling, after a rise in intracellular calcium and calcium-calmodulin binding. The iNOS isoform, which primarily is expressed in immune tissue and involves alternative calcium-independent mechanisms, is not perceived to be involved in normal penile erection.

In the science of NO related to penile erection, primary attention has thus far been given to the neuronal source of NO, whereas the endothelial source has been relegated to secondary importance as an auxiliary basis for producing NO for erectile function. The liberation of NO into the erectile tissue from nNOS requires neuronal depolarization resulting from electrical impulses transmitted neurally in response to psychogenic and reflexive erogenous stimuli that converge upon nNOS-containing efferent nerve fibers coursing within the corporal bodies. Facilitation of the neuronal release of NO in the penis may involve neuroactive amino acids such as glutamate and neuropeptides such as vasoactive intestinal peptide (Burnett, 1997). The intracorporal delivery of NO from eNOS has been perceived to involve mainly neurogenic stimuli that are transmitted through efferent nerves coursing within the erectile tissue that directly make contact with the endothelium. Acetylcholine, as well as other neurotransmitters such as substance P and bradykinin, is best characterized as stimulating NO release from endothelial sources in the penis (Kimoto et al, 1990; Knispel et al, 1991; Azadzoi et al, 1992; Hedlund et al, 2000b; Burnett et al, 2002). These neurotransmitters exert their effects by inducing a transient increase of calcium entry into endothelial cells, which briefly stimulates NO production by eNOS. Acute increases in "shear stress," the term used to describe pressure forces exerted on endothelial cells by the flow of blood over them, act to drive rapid but limited amounts of NO release by similar biochemical mechanisms (Burnett, 1997; Busse and Fleming, 1998).

Consistent with current notions that the constitutive NOS isoforms critically mediate penile erection, scientific findings have shown that pathologic disease processes associated with erectile dysfunction manifest decreased expression and/or activity of these enzymes (Burnett, 1997; Champion et al, 1999; Gonzalez-Cadavid and Rajfer, 2000; Akingba and Burnett, 2001).

Novel Concepts— The supposition that diverse mechanisms operate in the penis exerting precise regulatory control of NO release is entirely reasonable. Commonly accepted modulators of NO effects

in the penis conceivably include neurotransmitters, hormones, paracrine factors, and autocrine substances derived from the erectile tissue itself, besides exogenously administered agents. More recent considerations have extended to molecular mechanisms involved in the gene expression of the enzymes responsible for NO synthesis, which may actually adhere to a genitourinary-specific manner of control (Gonzalez-Cadavid et al, 2000). Further interest has centered on the roles of NOS-associated proteins, which could influence the intracellular transmission of the NO signal (Busse and Fleming, 1998; Gonzalez-Cadavid and Rajfer, 2000). Other areas that have generated great interest in yielding potential therapeutic approaches for erectile dysfunction include gene transfer and application of trophic effectors designed to augment NO biosynthesis in the penis (Garban et al, 1997; Champion et al, 1999; Bakircioglu et al, 2001).

A new direction in studying the biology of NO has determined that constitutive eNOS regulation can occur independent of transient calcium influx, as occurs with acute increases in shear stress or by acetylcholine stimulation, thereby permitting NO release in a sustained manner (Dimmeler et al, 1999; Fulton et al, 1999; Michell et al, 1999). The process for long-term production of NO from endothelial sources that can result from physical stimuli and biochemical signals has been described to involve other cellular components, including integrins, G proteins, and protein kinases (Busse and Fleming, 1998). Recently, it was discovered that sustained NO production in response to chronic shear stress and growth factor stimuli involves activation of phosphatidylinositol-3-kinase (P13-kinase) and its effector, the serine/threonine protein kinase Akt, which subsequently causes constitutive activation of eNOS (Dimmeler et al, 1999; Fulton et al, 1999; Michell et al, 1999).

This discovery has now been extended to the basic science of erection physiology, with an investigation showing that this protein kinase cascade physiologically mediates penile erection. Using rodent animal models, Burnett et al (2002) recently found that both electrical stimulation of the cavernous nerve and direct intracorporal vasoactive drug delivery elicited rapid increases in phosphorylated (activated) Akt and eNOS, which were blocked by wortmannin and LY294002, inhibitors of P13-kinase, the upstream activator of Akt (Hurt et al, 2002). These 2 drugs also markedly attenuated erectile responses. In addition, penile erection caused by intracorporal vasoactive drug delivery was profoundly reduced in mice with targeted deletion of eNOS. These findings led the investigators to postulate that the rapid, brief, calcium-dependent activation of nNOS initiates the erectile process, whereas P13-kinase/Akt-dependent phosphorylation of eNOS results in sustained NO production and thereby elicits full erection attainment (Table).

Clinical Therapeutics

NO-Based Therapy— The established importance of the NO-dependent regulatory system for penile erection has spurred approaches to stimulate this system for the treatment of erectile dysfunction, particularly that associated with defective NO regulation (Figure 2). Pharmacologic approaches advanced for consideration include synthetic NO donors explored for intracavernosal administration (Truss et al, 1994); L-arginine, the precursor amino acid for NO production, administered orally (Klotz et al, 1999); and nitrosylated alpha-adrenergic antagonists, under development for various possible routes of delivery (Saenz de Tejada et al, 1999). Gene therapies with NOS constructs have represented another exciting approach to alleviate erectile dysfunction (Garban et al, 1997; Champion et al, 1999). The recent initial description of a biochemical system producing activated constitutive NOS that regulates penile erection also has therapeutic implications (Hurt et al, 2002). Drugs that inhibit dephosphorylation of eNOS or that activate this enzyme or its upstream regulatory kinase, or alternatively, methods for gene transfer involving activated eNOS could offer novel therapeutic approaches for erectile dysfunction. A mechanistic basis for the angiogenic effects of statins involving Akt phosphorylation of eNOS in isolated vascular preparations (Brouet

et al, 2001) suggests that statin medications, for example, could have direct clinical relevance in the management of erectile dysfunction.

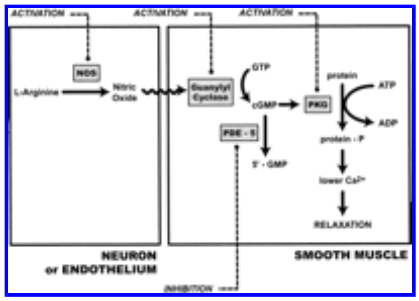

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Figure 2. Diagrammatic representation of potential molecular sites for therapeutic manipulation within the nitric oxide (NO)-dependent signal transduction system. The signaling cascade involves the production of the potent second-messenger molecule, 3', 5', cyclic guanosine monophosphate (cGMP), and its activation of protein kinase G (PKG), which elicits corporal smooth muscle relaxation by subsequent biochemical cascade. A plausible mechanism for the action of PKG is to induce phosphorylation changes of contractile proteins in combination with decreases in calcium levels for the effect. Tissue cGMP levels are determined by a balance between the activities of guanylyl (guanylate) cyclase, which catalyzes the formation of cGMP from guanosine triphosphate (GTP), and the cGMP-specific phosphodiesterase (PDE-5). PDE-5 catalyzes the breakdown of cGMP to the inactive form, 5'-GMP. The biochemical cascade offers multiple sites to regulate enzymes either by activation or inhibition, thereby influencing smooth muscle relaxation. ATP indicates adenosine triphosphate; ADP, adenosine diphosphate; P, phosphorylation; and Ca^{2+}, calcium. (Adapted with permission from Corbin and Francis, 1999.)

PDE-5 Inhibition— The NO-dependent signal transduction system required for penile erection involves a complex biochemical pathway in which several targets are available for pharmacologic manipulation. The most prominent one identified thus far is PDE-5, which enzymatically converts cGMP to its inactive form (Boolell et al, 1996; Turko et al, 1999). By its preservation, cGMP in turn is present to a greater extent than at baseline conditions to activate PKG, which then facilitates a cascade of biochemical events resulting in corporal smooth muscle relaxation and hence penile erection (Burnett, 1995; Boolell et al, 1996; Chuang et al, 1998; Turko et al, 1999; Hedlund et al, 2000a). This mechanism still requires the primary synthesis of cGMP, driven by NO production and release during sexual arousal. Therein lies the essence of the PDE-5 inhibitory mechanism for erection, that sexual stimulation and arousal are necessary for the therapeutic action of PDE-5 inhibitors. Succinctly, PDE-5 inhibitors augment, but do not cause, erection. This principle has clinical importance for the use of PDE-5 inhibitors to be effective in the management of erectile dysfunction. The fact that the PDE-5 enzyme is expressed in high concentrations in corporal smooth muscle of the penis compared with other structures of the body lends additional support to the value of PDE-5 inhibition as a therapeutic strategy for erectile disorders.

The biochemical mechanism of action of PDE-5 inhibitors as erectogenic agents is clinically relevant in the context of their therapeutic efficacy and safety profiles. The specific pharmacologic properties that refer to these concerns are the pharmacodynamics and pharmacokinetics of such agents (Corbin and Francis, 1999). With respect to pharmacodynamics, the biochemical potencies and selectivities of alternative PDE-5 inhibitors can be studied and compared. The biochemical potency refers to the capacity of the PDE-5 inhibitor to competitively bind to and block PDE-5 and is commonly described by its IC_{50}, the determinant defining the concentration of compound required to produce 50% inhibition of the enzyme. Accordingly, a lower IC_{50} of the compound implies its higher biochemical potency. The respective IC_{50} values in descending order (and hence ascending biochemical potency order) are 3.9, 0.94, and 0.7 nmol/L concentrations for sildenafil, tadalafil, and

vardenafil of the newly described PDE-5 inhibitor class of agents. Importantly, while the greater biochemical potency of a select PDE-5 inhibitor might suggest its proclivity toward superior clinical performance, only comparative clinical assessments permit such conclusions.

The biochemical selectivity refers to the capacity of the PDE-5 inhibitor to block PDE-5 relative to at least 10 other PDE enzymes in the PDE isoform family. This determinant is commonly presented as a selectivity ratio. Accordingly, a higher biochemical selectivity is assigned to the compound with a higher selectivity ratio. This concept relates to the compound manifesting reduced overlaps in specificity, or cross-reactivity, that might be associated with undesirable side effects. In this regard, PDE-5 inhibitor cross-reactivity with PDE-6, which is localized to the retina, is reported to occur with sildenafil, producing visual disturbances (Goldstein et al, 1998). Clinical trials with both vardenafil and tadalafil are also reported to cross-react but apparently less avidly with PDE-6, such that visual disturbances are reportedly even less common (Porst, 2002; Pryor, 2002). Other side effects commonly involving PDE-5 inhibitor therapy include headaches, facial flushing, dyspepsia, and rhinitis. These side effects are perceived to result from the inhibitory effects of PDE-5 present to some extent in tissues other than the corporal smooth muscle.

With respect to pharmacokinetics, the onset of action and the duration of action can be applied to characterize alternative PDE-5 inhibitors. T_{max}, the time to maximum plasma concentrations, is reportedly shorter for vardenafil (0.66 hour) than for sildenafil (1.16 hours) or tadalafil (2.0 hours) (Porst, 2002), suggesting that vardenafil offers a better opportunity for immediate drug efficacy. The half-life ($t_{1/2}$), the time required to eliminate or metabolize half the amount of drug, is reportedly 3.82, 3.94, and 17.5 hours for sildenafil, vardenafil, and tadalafil, respectively (Porst, 2002). The aspect of a longer half-life suggests that a drug has a potentially advantageous longer duration of action, although a prolonged half-life may also yield significant adverse effects and other adverse biochemical interactions.

Although the main focus in PDE-5 biology of the penis is to target its enzymatic activity for pharmacologic interventions for erectile dysfunction, new interest has been advanced with regard to regulating the expression levels of PDE-5 in the corpus cavernosum. Recent studies suggest that diverse mechanisms may exist for regulation of PDE-associated signaling in the penis (Kim et al, 2000; Gopal et al, 2001; Lin et al, 2001). Changes in PDE-5 substrate concentrations, the interplay of NO and cyclic nucleotide stimulatory systems, and the action of transcription factors affecting PDE-5 gene expression represent several aspects that deserve ongoing investigation with the development of PDE-5-based therapies. Besides considerations to modulate PDE-5 activity on a molecular level, some interest has been given to exploring pharmacologic synergism between PDE-5 inhibitors and other effectors of the erectile response. Early studies in animal models have shown that the combination of PDE-5 inhibitors with the central dopaminergic agent, apomorphine, or with the cyclic adenosine monophosphate (cAMP) inducer, prostaglandin E_1, potently stimulates penile erection (Andersson et al, 1999; Doherty et al, 2001).

Alternative Possibilities— An alternative molecular target of the NO-dependent signal transduction system for pharmacologically stimulating erections is guanylate cyclase. This enzyme, which is expressed in the corpus cavernosum, is conventionally described to be activated by NO for the synthesis of cGMP. A provocative, novel concept pertains to heightening guanylate cyclase activation to facilitate penile erection NO independently. In this light, the feasibility of agents that bind to the enzyme at an allosteric site different from the NO binding site and induce penile erection has been demonstrated (Brioni et al, 2002; Mizusawa et al, 2002). Most interestingly, while these agents may serve as independent effectors of cGMP production through guanylate cyclase

activation, they could effect a potentiated response from NO stimulation, with the chemical acting on the enzyme at a heightened activation state. Such considerations underscore that diverse opportunities can be explored on the basis of mechanisms of NO biology in the penis for the treatment of erectile dysfunction.

It is also intriguing to speculate that cGMP-dependent protein kinase (PKG) can be pharmacologically manipulated to a heightened activation state and thereby facilitate the NO-based biochemical cascade further downstream. Recent descriptions of autoinhibition of cyclic nucleotide-dependent protein kinase (Francis et al, 2002) suggest mechanistic possibilities not only to inactivate PKG (and likewise cAMP-dependent protein kinase A) but also potentially to facilitate its activity. It will be interesting to carry out additional evaluations of mechanisms involving protein kinases interacting with the NO-dependent signal transduction system in the penis, which may eventually translate as well into therapeutic utility.

Summary

In this brief review, the various aspects of the enzymology, biochemistry, and molecular pharmacology of the NO-dependent signal transduction system in the penis have been discussed. Scientific investigations of this system have certainly provided academic excitement while affording practical applications for the clinical management of erectile dysfunction. Recent and ongoing discoveries relating to this system may eventuate in the identification and manipulation of a host of molecular sites for therapeutic benefit.

Appendix

Question 1— Can you foresee in the future a combination therapy using different aspects of the guanylate-cyclase pathway to produce a more potent or synergistic effect?

Answer— It will be interesting to see how we can manipulate this guanylate-cyclase pathway using agents with different sites of action in order to enhance the effect. For example, if you look at guanylate-cyclase and some of the new compounds that are being developed, by binding to an allosteric site on guanylate cyclase, a better activational state for PKG activation can occur. But more interestingly, if NO is also present, there is an exponential effect in regard to cGMP production. This concept is very exciting in that various interactions within the pathway can lead to downstream effects to augment smooth muscle relaxation.

Question 2— The NOS knockout mice had reportedly sexually deviant behavior and aggression. Do you have any insight into this behavior or its cause?

Answer— In regard to the aggressive behavior reported in some nNOS knockout mice, this has not been significant as with endothelial NOS knockout. Aggressive behavior is not related to penile erection, but it may have something to do with brain mechanisms of aggression, which is certainly distinct from what we are working on at this time.

Question 3— Are you aware of any new research on NO-releasing compounds?

Answer— Many groups are trying to develop novel NO-releasing agents. These NO donors or nitrosylated agents may, in combination, augment the smooth muscle relaxing effect. Frankly, that part of the system has not really demonstrated as substantial an efficacy as has been shown with other downstream enzyme systems.

Question 4— Recently, there was an article published in JAMA claiming a protective effect by

PDE-5 inhibitors. Before, this family of enzymes was considered dangerous to vasculature and to people with heart disease. These recent studies on large cohorts of men actually show fewer myocardial infarctions (MIs) and greater longevity. Do you think these PDE-5 inhibitors may benefit some men with specific vascular conditions that predispose them to early death?

Answer— The data are somewhat circumstantial if you review these recently reported series. It appears that for some men on the drug, there were fewer adverse vascular effects, including MIs. What is the science behind this? Possibly, there is some remodeling of the vascular system of the penis when there is an increased blood flow. This may have some relevance in regard to examining why PDE-5 inhibitor therapy may cause long-term benefits in restoring erectile function. It has been described in a number of recent reports, with currently available drug therapy, that some men discontinue use of the drug because of significant improvements in spontaneous activity. This is very exciting and suggests that the science needs to evolve further in this field to explore some of these different medical issues.

Footnotes

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