PRESENTATIONS AND REPORTS

Nitric Oxide in the Penis—Science and Therapeutic Implications from Erectile Dysfunction to Priapism

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Perhaps as much as any other subspecialty of urology, sexual medicine has undergone a wondrous evolution in the past 10–20 years. Great advances have been made generating from the study and discovery of molecular mechanisms governing diverse sexual functions. This observation is particularly relevant to the field of erection physiology. Our patients with erectile dysfunction have benefited accordingly as recipients of improved therapies along with optimized management strategies, from which they have gained increasingly healthful and high-quality lives. Undoubtedly, the developments related to the study of nitric oxide in the biology of the penis have taken center stage amid this progress. Nitric oxide, an evanescent seemingly trivial gaseous chemical, has been quite a force in bringing the sphere of sexual medicine forward. Widely acknowledged at this time is the fact that nitric oxide subserves a fundamental mechanism responsible for the erectile response. This knowledge has been translated into successful pharmacotherapy, as demonstrated by the creation of oral phosphodiesterase type 5 (PDE5) inhibitor therapy (i.e., sildenafil, tadalafil, vardenafil), based on nitric oxide signaling in the penis, for the treatment of erectile dysfunction.

At the most recent Sexual Medicine Society of North America fall meeting in New York City (November 17–20, 2005), I was privileged to have had the opportunity to deliver a keynote address celebrating the historical beginnings and highlights of nitric oxide research in the penis. My sense of honor reflected an awareness of the tremendous fortune I have had in being a major investigator of this exciting scientific field, and furthermore gratitude I owed for this recognition. I sincerely believe that many contributors to this field are too deserving of recognition and might otherwise be nominated to reminisce on this topic. I also express my appreciation to Dr. Irwin Goldstein, editor-in-chief of our journal, who by requesting that I prepare a composition based on the lecture for inclusion in the journal has allowed my thoughts to acquire a lasting form.

An early description of the physiologic role of nitric oxide specified this chemical to be a vascular smooth muscle relaxant, and in fact it was early termed endothelial-derived relaxing factor [1,2]. The identification of nitric oxide as a major player in vascular smooth muscle relaxation and later in the erection response circa 1990–92 is properly credited to the collaborative team of Dr. Louis Ignarro and Dr. Jake Rajfer at University of California, Los Angeles (UCLA) [3–5]. These investigators in applying organ bath experimental methodology showed that isolated rabbit and human corporal tissue strips relaxed under the influence of the chemical. Their clever in vitro experiments fundamentally were the demonstration that nitric oxide or its precursor L-arginine elicited tissue relaxation and, conversely, neurostimulated tissue relaxation was blocked by inhibitors of nitric oxide synthesis. Many other

investigators also demonstrated similar in vitro findings [6–9]. Critical in vivo evidence that nitric oxide regulated penile erection resulted from further study, including work conducted in my laboratory, affirming the importance of nitric oxide as the elusive erection mediator [10–13].

The identity of the relaxant factor governing physiologic penile erection had early been a matter of much consternation [14]. My laboratory was instrumental in showing that nitric oxide derived from nerves coursing within the erectile tissue such that it served as an atypical neurotransmitter regulating the erectile response [13,15]. The discovery followed an interaction I had fostered with Dr. Solomon Snyder, Director of Neuroscience at Johns Hopkins University in 1991. Just prior to that time, Dr. Snyder's group had elucidated a neurotransmitter-like role for nitric oxide [16]. In fact, his laboratory had cloned the neuronal nitric oxide synthase gene and developed probes to localize this synthetic enzyme in various neuronal tissues including the brain and portions of the peripheral nervous system [17,18].

During my initial interactions with Dr. Snyder in the early course of my urological residency training, I recounted my dismay that the clinical options for erectile dysfunction were few and basic, compromised by an incomplete understanding of the scientific mechanisms underlying penile erection. I presented my thoughtful but nonetheless off-the-wall notions that clues about erection physiologic mechanisms might be revealed by studying a model of erection excess, priapism. I also shared my conjecture at that time that a nitric oxide regulatory disturbance in the penis might account for a predominant form of priapism, priapism related to sickle cell disease. This proposal reflected emerging knowledge then that hemoglobin binds nitric oxide and effectively causes its inactivation [19]. (Somewhat interestingly, the association of nitric oxide in the penis with relevance to priapism has only recently become a central area of study in my laboratory, now many years later). To proceed in this area of study, Dr. Snyder directed me to work alongside Dr. David Bredt and Dr. Charles Lowenstein, a graduate student and a postdoctoral fellow, respectively, working in his laboratory. We began our investigative venture, applying molecular tools which localized nitric oxide synthase-containing nerves in the penis while also establishing a neuroregulatory role for nitric oxide in physiologic penile erection.

Soon after this discovery, mice genetically engineered to be deficient in nitric oxide synthase genes were developed, offering opportunities to probe further the roles of nitric oxide synthase genes in various physiological contexts. In collaborating with the team originating these mice, Dr. Paul Huang and his colleagues at the Massachusetts General Hospital, we initiated studies examining specifically the erectile ability of these transgenic mice. Our studies began using mice lacking the neuronal form of the gene, expecting that these mice would not have functional erections. However, much to our surprise, these mice retained erection ability! Our initial explanation for this phenomenon was that erection preservation in the absence of neuronal nitric oxide synthase resulted from an upregulation of the endothelial form of the enzyme acting compensatorily [20]. We then learned that neuronal nitric oxide synthase gene variants existed and neuronal nitric oxide synthase-deficient mice only lacked the main alpha variant of the gene, retaining an alternative variant or variants in the penis [21]. We now have clarified that the neuronal nitric oxide synthase beta variant is functional as an erection mediator [22]. This knowledge has combined with work by others affirming the requirement of the nitric oxide signaling pathway in penile erection [23].

Further interests in this field during the 1990s increasingly turned toward its clinical ramifications as well as concepts that the nitric oxide signaling pathway in the penis could be exploited for therapeutic purposes. A much heralded development was the development of PDE5 inhibitors for the treatment of erectile dysfunction, as the medications originally were directed as treatment for angina. This redirection arose in a large part from the realization that the chemical pathway and its regulatory features such as PDE5 significantly influence the erectile response. Many investigators showed that aberrant nitric oxide signaling in the penis could explain a variety of forms of erectile dysfunction [24–33] and multiple regulatory factors (e.g., androgen milieu, glycosylation end-product presence, cofactor availability) influenced the effects of this signaling pathway [25–28,34–36]. My laboratory was fortunate to extend our collaborative efforts with Dr. Rajfer and Dr. Nestor Gonzalez-Cadavid at UCLA. Together with these investigators, we helped establish the importance of co-regulatory proteins in the actions of neuronal nitric oxide synthase in the penis [37].