

# The Molecular Basis of Erectile Physiology: From Bench to Bedside

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For centuries, sexual medicine was a taboo subject practiced by quasiscientists, back-alley charlatans, and village shamans. Because of a paucity of basic knowledge about the anatomy, physiology, and pharmacology of the erectile process, many myths on causation and therapy were promulgated through time (Hellstrom, 1999).

The impetus of the National Institutes of Health (NIH) Consensus Development Conference on Impotence in 1992 was to educate health care providers and to familiarize the public on aspects of human sexuality, sexual dysfunction, and the availability of successful treatments (NIH Consensus Development Panel on ED, 1993). An invaluable offshoot from this conference was establishing a universal definition for erectile dysfunction (ED) as a condition in which penile erection is insufficient for vaginal penetration for the mutual sexual satisfaction of both partners.

The Massachusetts male aging study (MMAS) provided information on the prevalence of ED in a general population of 1290 noninstitutionalized men aged 40 to 70 years (Feldman et al, 1994). Using validated questionnaires, this study demonstrated that the prevalence of ED was much higher than previously perceived. Baseline data from the MMAS showed that the combined prevalence of minimal, moderate, and complete ED was more than 50% in American men. Using the United Nations projected male population distributions for 2025, the prevalence rates for ED were applied to the MMAS. In 1995, it was estimated that 152 million men worldwide experienced ED, and the projections for 2025 show a prevalence of 320 million, an increase of nearly 170 million men (Aytac et al, 1999).

The magnitude of this condition has stimulated the funding of basic and clinical research in ED, and our knowledge base continues to expand. Penile erection is a neurovascular event influenced by cortical and hypothalamic activities. The hemodynamic changes involve increased arterial flow, re-

laxation of the smooth muscle in the sinusoidal spaces, and increased venous resistance. Cavernosal smooth muscle relaxation is central to the erectile process.

In the early 1990s, the nitric oxide-cyclic guanosine monophosphate system was recognized to be the principal mediator of the erectile process (Burnett et al, 1992; Rajfer et al, 1992).

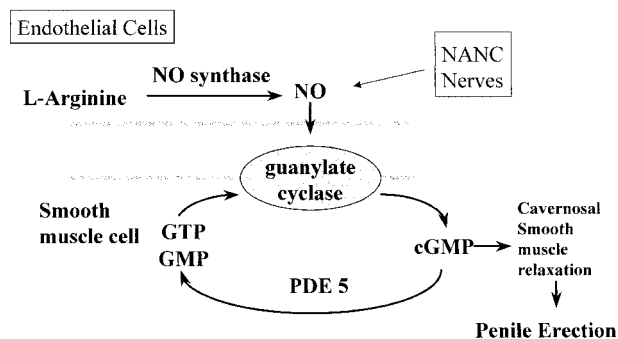
There is an ensuing biochemical cascade that ultimately reduces the level or changes the sensitivity of free intracellular calcium to induce smooth muscle relaxation (Figure).

Since that time, there has been further appreciation of the influence by other endogenous neurotransmitters, ions, autocooids, paracrine factors, and hormones in the regulation of the erectile process. In one of the first applications in the new field of gene therapy, Christ et al (1998) pioneered the use of naked DNA as a vector for the delivery of maxi-K channel genes to the corporal myocytes of the penis. In early studies in diabetic and aged rat models, following a single injection of the plasmid containing the human recombinant gene hSlo, this strategy was shown to be effective for up to 4 to 6 months.

In more recent works, Mills et al (2001) have focused on pathways that normally cause vasoconstriction (Rho/Rho-kinase system) of the cavernosal smooth muscle and allow for penile flaccidity. By using specific blockers of this anti-erectile pathway, vasodilation and erections can occur.

The following 3 manuscripts from this unique symposium explore the molecular basis of erectile physiology

## Nitric Oxide-cGMP Mechanism of Action: Physiology of Erection



Nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) mechanism of action: physiology of erection.

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and illuminate a number of unique signal-transduction pathways that stimulate cavernosal smooth muscle relaxation and subsequent penile erection. Naturally, all such hypotheses will need to undergo further investigation, re-study over time by other researchers, and ultimately, clinical confirmation. Notwithstanding, molecular research on the erectile mechanism will undoubtedly lead to further innovation and discovery. Basic investigation in this rapidly evolving field will undoubtedly pave the way for tomorrow's cures.

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