Nitrergic Mechanisms for Management of Recurrent Priapism

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DOI: 10.1002/smrj.56

ABSTRACT

Introduction. Priapism is a condition involving prolonged penile erection unrelated to sexual interest or desire. The ischemic type, including its recurrent variant, is often associated with both physical and psychological complications. As such, management is of critical importance. Ideal therapies for recurrent priapism should address its underlying pathophysiology.
Aim. To review the available literature on priapism management approaches particularly related to nitrergic mechanisms.
Methods. A literature review of the pathophysiology and management of priapism was performed using PubMed.
Main Outcome Measure. Publications pertaining to mechanisms of the molecular pathophysiology of priapism.
Results. Nitrergic mechanisms are characterized as major players in the molecular pathophysiology of priapism. Phosphodiesterase type 5 inhibitors represent an available therapeutic option with demonstrated ability in attenuating these underlying nitrergic derangements. Several additional signaling pathways have been found to play a role in the molecular pathophysiology of priapism and have also been associated with these nitrergic mechanisms.
Conclusion. An increasing understanding of the molecular pathophysiology of priapism has led to the discovery of new potential targets. Several mechanism-based therapeutic approaches may become available in the future. **Anele UA and Burnett AL. Nitrergic mechanisms for management of recurrent priapism. Sex Med Rev 2015;3:160–168.**

Key Words. Nitric Oxide; Recurrent Ischemic Priapism; Therapy

Introduction

Priapism is a pathological condition involving penile erection persisting beyond or in the absence of sexual arousal or desire [1]. Estimates of the incidence rates of this disorder among the general population have widely ranged between 0.34 and 5.34 per 100,000 men per year, with the higher rates observed in patients aged 40 and older [2–4]. Priapism, specifically the ischemic type, has been observed to disproportionately affect certain populations, notably patients with sickle cell disease (SCD), in whom prevalence rates as high as 40% have been observed [5,6]. SCD patients are at particular risk of experiencing repeated yet self-limited episodes, termed recurrent ischemic priapism (RIP) or stuttering priapism [1]. Despite the transitory nature of these episodes, which typically last less than 3 hours in duration, RIP may herald major ischemic episodes in 30–50% of cases [1,5–7].

Ischemic priapism is associated with severe complications, such as erectile dysfunction (ED), resulting from erectile tissue ischemic damage, particularly after episodes lasting greater than 36 hours [5,6,8–10]. Although shorter in duration, RIP episodes have also been associated with a significant risk of ED, with rates ranging from 29% to 48% [5–7]. Therefore, the management of recurrent episodes is essential in order to prevent or at least reduce possible cavernosal tissue damage and the risk of progression to major ischemic episodes. Here, we review emerging molecular mechanisms, specifically relating to the

nitrergic pathway, which can be expected to guide current and future therapeutic options for the management of recurrent priapism.

Normal Erection Physiology

Penile flaccidity is controlled by vasoconstrictive factors that maintain vascular and smooth muscle tone in the basal state [11,12]. Inhibition of this contractile state, resulting in erection, can occur with genital stimulation, psychosocial excitement, or REM sleep [13]. During erection, smooth muscle relaxation occurs and permits increased arterial blood inflow and expansion of erectile tissues, which decreases venous outflow and sustains penile engorgement [14,15]. The nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway is now recognized to be the critical component in the complex coordination of vasorelaxant and vasoconstrictive mechanisms involved in normal erection physiology [16,17].

The NO synthase (NOS) enzyme is the principal mediator of NO synthesis and regulates the vascular and neurogenic pathways involved in penile erection. The initiation and maintenance phases of penile erection are regulated by neuronal NOS (nNOS) and endothelial NOS (eNOS), constitutive enzyme isoforms found in nerve terminals and vascular endothelium, respectively [18]. Phosphorylation of these NOS isoforms results in their activation, whereby NO is generated from the substrate L-arginine [19]. Subsequently, NO locally diffuses into smooth muscle cells and binds to the iron substrate within the heme moiety of guanylate cyclase (GC) [20]. Upon activation, GC converts guanosine-5′-triphosphate to cGMP, regulating the downstream activation of cGMP-dependent protein kinase G that generates cavernosal smooth muscle relaxation and thus penile erection [20]. Termination of the erectile response occurs through the enzymatic activity of cGMP-specific type 5 phosphodiesterase (PDE5), which hydrolyzes the 3′5′ bonds of cGMP, converting it to its inactive state 5′-GMP [21].

Nitrergic Mechanism of Recurrent Priapism

Over 95% of priapism presentations are caused by the ischemic priapism type and are hallmarked by stagnant cavernous blood flow, corporal rigidity, and pain [1,10]. The repetitive and self-remitting episodes of RIP, an ischemic variant, typically last less than 3 hours in duration [10,22]. As RIP is found to be significantly prevalent among patients with hematological disorders, particularly SCD, erythrocyte sludging and vascular stasis were described classically to constitute the primary etiology [9]. Advances in the field have increasingly uncovered more complex molecular mechanisms underlying RIP. Recent investigations have identified decreased NO bioavailability, common in the setting of hematological disorders such as SCD [23], to be a key factor in the etiology of priapism [24].

Disruption of the NO signal transduction pathway, the main erection mediatory system regulating penile erection, has recently been identified to be the principal mechanism underlying the pathophysiology of priapism [24]. Transcriptionally downregulated PDE5 expression and activity consequent to basally decreased levels of its regulator, cGMP, is the fundamental determinant; without PDE5 function, erections are uncontrolled [24]. Several possibilities exist for yielding functionally decreased cGMP, which is related to a chronic decrease in upstream production of endothelium-derived NO. Vasculopathic damage associated with SCD may lead to a quantitative loss of eNOS, a source of decreased NO bioavailability [24–27]. Through the release of free hemoglobin, an avid scavenger of intravascular NO, hemolysis may also contribute to reducing NO bioavailability. The release of arginase, which reduces L-arginine (a substrate for NO synthesis), and excess production of reactive oxygen species (ROS) (a chronically present state in SCD) may also interfere with the generation and function of endothelium-derived NO [28–30]. The decrease in cGMP production resulting from reduced NO bioavailability leads to a compensatory decrease in cGMP-dependent expression and activity of PDE5 [24,31].

Although deficiency of endothelium-derived NO reduces basal levels of cGMP, the neuronal source of NO, nNOS, remains intact. Thus, upon neurological initiation of penile erection (i.e., occurring during REM sleep or sexual activity), neuronally derived NO can transiently drive cGMP production and accumulation, producing cavernosal tissue relaxation. Because of decreased basal function of PDE5, normal regulation of the erection does not occur, resulting in priapism.

Nitrergic Mechanisms of Management (Figure 1)

The physical and psychosocial complications of recurrent priapism can be devastating. Therefore,