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Review

Treatment of erectile dysfunction: New targets and strategies from recent research

K. Decaluwé, B. Pauwels, C. Boydens, J. Van de Voorde *

Department of Pharmacology, Ghent University, Ghent, Belgium

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ABSTRACT

In recent years, research on penile erection has increasingly been centered on the molecular mechanisms involved. Major progress has been made in the field and at present a whole number of neurotransmitters, chemical effectors, growth factors, second-messenger molecules, ions, intercellular proteins, and hormones have been characterized as components of the complex process of erection. This knowledge has led to the discovery of several new therapeutic targets and multiple medical approaches for the treatment of erectile dysfunction (ED). This review focuses on the progress made in this field within the last few years.

Contents

* Corresponding author at: Department of Pharmacology, De Pintelaan 185-Blok B (2nd floor), 9000 Ghent, Belgium. Tel.: +32 9 332 33 42; fax: +32 9 332 89 66.
E-mail address: johan.vandevoorde@UGent.be (J. Van de Voorde).

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1. Introduction

Erectile dysfunction (ED) is highly prevalent affecting almost 50% of men in the 40–70 year age range, which corresponds to approximately 150 million men worldwide (Mesquita et al., 2012). ED is generally considered as a manifestation of a functional and/or structural abnormality affecting the penile circulation. Although modifying lifestyle risk factors can help, in most cases patients also need medication to improve or correct ED (Glina et al., 2012). Phosphodiesterase type 5 (PDE-5) inhibitors have revolutionized the treatment of ED. However, despite their efficacy, they have limitations (Park et al., 2013; Shamloul and Ghanem, 2013). Especially patients suffering from diabetes and nerve-injury show a poor response to PDE-5 inhibitors or become refractory (Chung and Brock, 2011).

In recent years a huge number of studies have been published aiming to find new therapeutic strategies for the treatment of ED. Since the literature on therapeutic targets has often been reviewed in recent years (Albersen et al., 2010b; Andersson, 2011; Burnett et al., 2010; Chung and Brock, 2011; Decaluwe et al., 2011; Feifer and Carrier, 2008; Hatzimouratidis and Hatzichristou, 2008; Williams and Melman, 2012), the present review focuses on the studies published since 2010. Innovative ED therapies aim to treat underlying microvascular abnormalities, to restore the smooth muscle contractility, to prevent cavernosal fibrosis, to promote endothelial revascularization, to modulate neurohormonal pathways and/or to regenerate new penile tissue (Chung and Brock, 2011).

2. New therapeutic targets

2.1. Targets associated with vasorelaxation induced by the NO–cGMP pathway

The NO–cGMP pathway plays a critical role in corpora cavernosa (CC) smooth muscle relaxation and penile erection. A remedy for ED would be to preserve or strengthen the activity of the NO–cGMP pathway. This is already indicated by the success of PDE-5 inhibitors, which inhibit the breakdown of intracellular cGMP. In addition, intervening with the NO–cGMP pathway at levels other than the PDE-5 enzymes also improves erectile function both in animals and humans (Leite et al., 2007).

2.1.1. Upregulating NO production

Considering the essential role played by NO in the physiology of erection, strategies aiming to increase endogenous NO concentrations are among the most attractive therapies for patients suffering from impotence.

2.1.1.1. L-arginine. One such strategy is to enhance the L-arginine concentration which is the substrate for NO synthases (NOS). However, the level of efficacy reached by the chronic use of L-arginine monotherapy remains uncertain. Recently, L-arginine aspartate–adenosine monophosphate (AMP) combination therapy was shown effective in patients with mild-to-moderate ED (Neuzillet et al., 2013). A synergistic effect of AMP and L-arginine was previously also demonstrated in male rabbit CC tissue (Hupertan et al., 2012). In addition, a recent publication demonstrated that argirein, which releases rhein (a compound purified from Radix et Rhizoma Rhei) and L-arginine after medication, alleviates corporal dysfunction in diabetic rats through normalizing the abnormalities of NOS and suppressing corporal inflammation (Cheng et al., 2013). These data indicate that L-arginine, especially in combination with other pro-erectile agents could be useful in the treatment of ED. However, oral L-arginine supplementation does not significantly increase L-arginine blood levels because of the hepatic first-pass effect or metabolization by intestinal bacteria. Therefore, L-citrulline supplementation might be more effective than L-arginine supplementation, since L-citrulline is neither affected by the hepatic first-pass effect nor is it metabolized by intestinal bacteria and L-citrulline is converted to L-arginine in the kidney. Indeed, a recent study demonstrated that oral L-citrulline supplementation improves erectile function in rats with acute arteriogenic ED (Shiota et al., 2013). Moreover, a clinical trial also reported that the oral supplementation with L-citrulline improves mild forms of ED (Cormio et al., 2011).

2.1.1.2. Arginase. Given that L-arginine is the common substrate for both NOS and arginase, elevation of arginase activity can limit availability of L-arginine for NOS, thereby reducing NO production and impairing vascular function. Previous studies indicate that increased arginase expression and activity are associated with aging and diabetes-related ED (Ilies et al., 2011; R. Segal et al., 2012). A reduction of arginase activity in the penis *via* gene knockout or arginase inhibition *in vitro* and *in vivo* has been shown to improve endothelial function and to restore erectile responses (Bivalacqua et al., 2007; R. Segal et al., 2012; Toque et al., 2011). Additionally, pretreatment of diabetic CC with inhibitors of arginase (ABH) partially prevented impairment of NO-mediated corporal relaxation and elevation of arginase activity (Toque et al., 2013). Of interest, increased production of urea and ornithine by arginase has been shown to lead to vascular hyperplasia and fibrosis (R. Segal et al., 2012). Thus the improved erectile responses observed after arginase inhibition may not only be related to an increase in NOS activity but also with a reduction in collagen deposition and fibrosis.

2.1.1.3. Extracellular signal-regulated kinase (ERK). ERKs are well known to mediate cellular responses initiated by growth factors. Recently it has been suggested that they also play a role in vascular reactivity (Carneiro et al., 2008b). ERK seems to phosphorylate and reduce eNOS activity, including in human cavernosal tissue (Sommer et al., 2002). Furthermore, patients with ED exhibit more active ERK in the cavernosal smooth muscle than patients without ED (Sommer et al., 2002). Moreover, recent data demonstrate increased ERK1/2 in CC from deoxycorticosterone acetate (DOCA)-salt and Ang-II hypertensive mice, as well as in CC from diabetic mice (Labazi et al., 2013). In addition, inhibition of ERK improves cavernosal relaxation in diabetic mice and abolishes the enhanced contraction to endothelin-1 (ET-1) in CC in hypertension (Carneiro et al., 2008a; Nunes et al., 2011).

2.1.1.4. Asymmetric dimethylarginine (ADMA). Another way to increase intracellular NO concentrations is by inhibiting the endogenous NOS competitive inhibitor asymmetric dimethylarginine (ADMA), a L-arginine analog. The majority of ADMA is metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) (Palm et al., 2007). However, intracellular ADMA that escapes metabolism by DDAH may reduce NOS activity. Moreover, a reduced activity of DDHA has already