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# Mechanisms in Erectile Function and Dysfunction: An Overview

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## 1. Introduction

Erectile dysfunction (ED) is a widespread problem affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. Over 30 million men suffer from ED in the U.S. <sup>1</sup> and it is becoming a public health issue. The prevalence of ED is very high and is expected to raise considerably over the next 25 years, impacting more than 300 million men by 2025 <sup>2</sup>. ED is defined as the persistent inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance. Its etiology is multifactorial. Various aspects affect the expression/degree of ED and risk factors include age, diabetes mellitus, neurologic diseases, smoking and cardiovascular diseases (CVD), among others <sup>3</sup>. Although the disorder has been described for more than 1000 years, the molecular basis and mechanisms of ED have yet to be completely understood. In the last 4 decades, elucidation of the macroscopic structures of the erectile system <sup>4-5</sup> ushered in a new era of therapeutic options for erectile disorders. Later, new insights into erectile neurotransmission, <sup>6</sup> essentially the nitric oxide (NO) pathway, <sup>7</sup> resulted in rational alternatives as a treatment <sup>8</sup>. Nowadays, advances in gene discovery and intensive research regarding different mechanisms which could lead to ED have increased the working knowledge of the pathways involved in this condition. This chapter will describe the basic penile physiology and the emergent mechanisms associated to pathophysiology of vasculogenic ED. Penile anatomy and physiology will be summarized in order to review the new insights regarding pathways and critical modifications observed in ED condition.

## 2. Penile anatomy

The penis is composed of three bodies of erectile tissue running in parallel; the corpus spongiosum, encompassing the urethra and terminating in the glans penis; and the two corpora cavernosa (CC) which function as blood-filled capacitors providing structure to the erect organ <sup>9</sup>. The penile CC are highly specialized vascular structures that are morphologically adapted to their function of becoming engorged during sexual arousal. The trabecular smooth muscle constitutes approximately 40-50% of tissue cross-sectional area, as assessed by histomorphometric analysis <sup>10</sup>. There are three main arteries in the penis: cavernosal, dorsal, and bulbourethral. All three arise from a shared branch of the internal pudendal artery and provide an extensive anastomotic network <sup>11</sup>. Nowadays, there is a tendency to perform *in vitro* experiments using the pudendal artery instead of cavernosal

tissue to investigate pathophysiological aspects of ED since this artery is the major resistance to penile engorgement during sexual stimulation. Novel findings suggest that the pudendal artery contributes 70% of the total penile vascular resistance<sup>12</sup>. The arterial blood supply in the CC is mainly fed from the deep penile cavernosal artery<sup>9</sup>, which causes corporal enlargement during erection, whereas the deep dorsal artery causes glans enlargement. Venous drainage is not similar to arterial supply; there exists only one deep dorsal vein that runs alongside the dorsal arteries and nerves in Buck's fascia above the tunica albuginea, which is a multilayered structure where emissary veins pass. The human penile venous system is generally described as a single deep dorsal vein accompanied by a pair of dorsal arteries positioned between the tunica albuginea and Buck's fascia for the venous drainage<sup>13</sup>. The corpus spongiosum is erectile tissue analogous to CC, but with a thinner tunica albuginea. The urethra lies within the spongiosum. The innervations of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter in the CC and corpus spongiosum to affect the neurovascular events during tumescence and detumescence<sup>14</sup>.

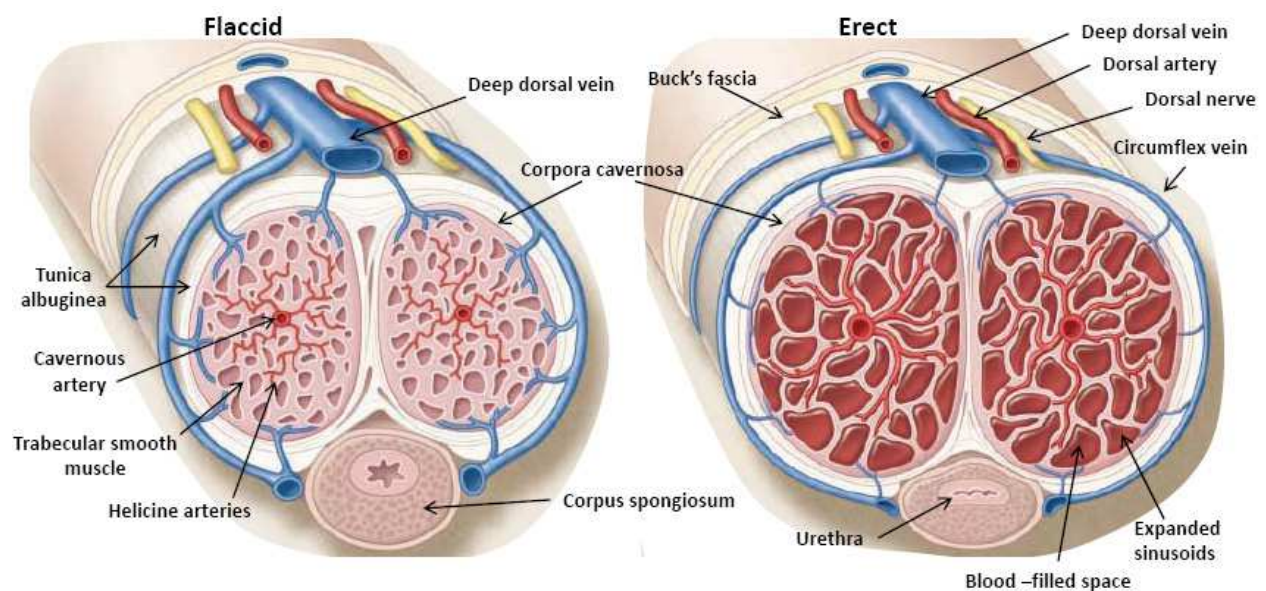


Fig. 1. Penile anatomy. Adapted from Fazio and Brock, 2004.<sup>15</sup>

### 3. Physiology of Penile Erection

Penile erection (PE) involves central and peripheral pathways. Tumescence is initiated after central processing and integration of tactile, visual, olfactory and imaginative stimuli. Upon sexual stimulation, signals are generated to the peripheral tissues involved. Thus, final response is mediated by coordinated spinal activity in the autonomic pathways to the penis, and also in the somatic pathways to the perineal striated muscles. Both central and peripheral regulation of PE involves several neurotransmitters and systems, of which details are still not completely known. Spinally, there seems to be a network consisting of primary afferents from the genitals, spinal interneurons, sympathetic, parasympathetic and somatic nuclei, which is capable of integrating all information. Peripherally, the balance between substances that control the degree of contraction of the cavernosal smooth muscle

determines the functional state of the penis <sup>16</sup>. The dynamic interplay of vasoconstrictors and vasodilators in the penis establish the erect or flaccid state.

PE is determined by pressure changes in the cavernosal arterioles and sinuses. The vasculature of the erectile mechanism differs from most vascular beds as it is composed of arterioles and hollow blood-filled sinuses, both which are lined with smooth muscle and endothelial cells <sup>14</sup> as previously described. In the flaccid state, this tissue is tonically contracted, allowing only a small amount of arterial flow for nutritional purposes. The partial pressure of oxygen (PO<sub>2</sub>) in the blood is around 35mmHg <sup>17</sup>. On the other hand, dilation of the penile arteries is the first event in the development of erection. Its consequence is the increase of blood flow and pressure into the lacunar space. Then, the expansion of sinusoids blocks the incoming blood. Also, venous outflow is reduced by compression of venular spaces between the tunica albuginea and peripheral sinusoids. This stretches the tunica to its capacity and decreases the venous outflow to a minimum, leading to an increase in intracavernosal pressure, which is maintained at approximately 100mmHg (2). Thus, erection includes sinusoidal relaxation, arterial dilation and venous compression (3).

### 3.1 Mechanisms mediating erection and penile relaxation

In general, mechanisms leading to normal erectile function imply inter-connections among neurons, striated perineal muscles and androgens which are responsible for maintaining sexual behavior in adults. Locally, the stage of penile erection requires relaxation of cavernosal smooth muscle. It is triggered by release of substances from parasympathetic and non-adrenergic non-cholinergic nerves (NANC), which in turn promotes vascular and cavernosal relaxation, leading to an increase in blood flow and intracavernosal pressure resulting in erection (Figure 1). Although several vasodilators have been implicated in this process, nitric oxide (NO) still is the main vasodilator involved <sup>18-19</sup>. In the penis, stimulation of parasympathetic nerves inhibits noradrenalin release and evokes acetylcholine (Ach) release, which binding to muscarinic receptors in endothelial cells promoting eNOS activation and consequently NO production. Cholinergic nerves have been demonstrated within the human cavernous smooth muscle and surrounding penile arteries and ultrastructural examination has also identified terminals containing cholinergic vesicles in the same area <sup>20</sup>. Two decades ago, it was suggested that NO released from NANC increases the production of 3',5'-cyclic guanosine monophosphate (cGMP), which in turn relaxes the cavernosal smooth muscle <sup>7, 21</sup>. Nowadays, it is well known that NO plays a critical role in erectile function. NO is formed from the precursor amino acid, L-arginine, by enzymatic action of NOS, which exists as three main isoforms: neuronal NOS (nNOS), inducible (iNOS), and endothelial NOS (eNOS). All three isoforms have been detected in the penis, although nNOS and eNOS are the main constitutively active NOS enzymes expressed in penile tissues <sup>22</sup>, it is activated by calcium entry into the cell, binding to calmodulin associated with enzymes <sup>23</sup>.

There are two main intracellular mechanisms for relaxing the cavernosal smooth muscle: the guanylate cyclase (GS)/cGMP and adenylate cyclase/cAMP pathways (Figure 3). NO is associated with GS/cGMP signaling, called NO/cGMP pathway. Upon its release, NO diffuses locally into adjacent smooth muscle cells of the corpus cavernosum and binds to soluble guanylyl cyclase (GC), which catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. This cyclic nucleotide then activates protein kinase G, also known as



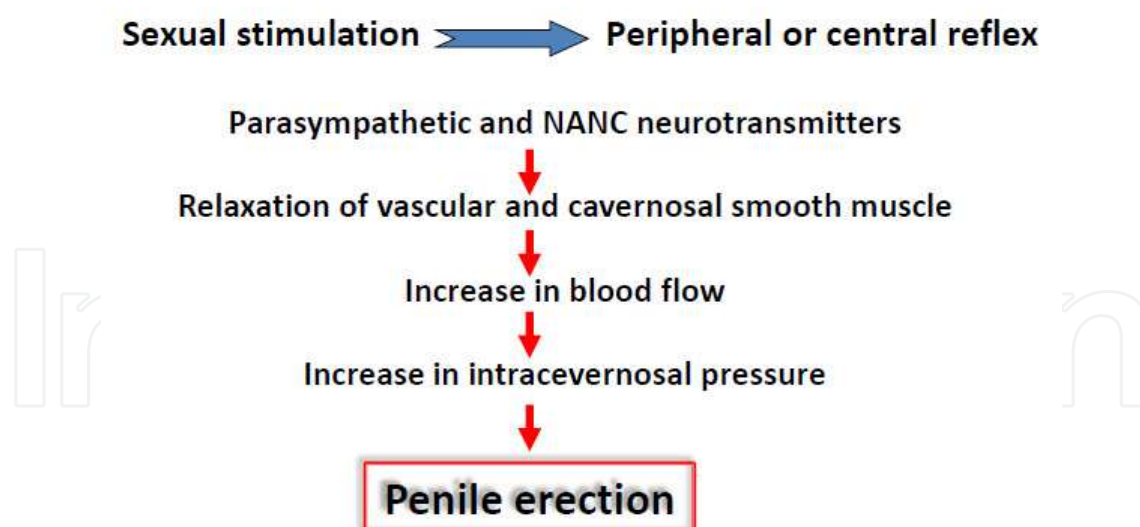


Fig. 2. Sequence of events required for penile erection. Upon sexual stimulation, substances such as Ach and NO are released from endothelial cells, parasympathetic and NANC neuronal endings evoking vascular relaxation and consequently increase in blood flow. Thus, there is an increase in intracavernosal pressure resulting in penile erection.

cGMP-dependent protein kinase I (cGKI), which decreases cytosolic  $\text{Ca}^{2+}$  by various mechanisms. cGMP also blocks RhoA migration avoiding Rho-kinase pathway activation, which is a step very important to penile relaxation. The decay in cytosolic  $\text{Ca}^{2+}$  concentration induces relaxation of the vascular and cavernosal smooth muscle cells, leading to dilation of arterial vessels, increased blood flow into the corpora cavernosa, and penile erection (Figure 3). Contributing to penile relaxation, substances such as prostaglandin E1 (PGE1) can bind to G protein coupled receptors and activate the enzyme adenylate cyclase, which catalyzes the conversion of adenosine monophosphate (AMP) to cyclic AMP (cAMP). This cyclic nucleotide activates protein kinase A (PKA), which also decreases the intracellular  $\text{Ca}^{2+}$ . PGE1, injected intracavernosally, alone or in combination, is today the second-line treatment for ED <sup>24</sup>. These second messengers, cGMP and cAMP activate protein kinase (PKG and PKA respectively), which in turn phosphorylate certain proteins and ion channels, resulting in opening of the potassium channels and hyperpolarization, sequestration of intracellular  $\text{Ca}^{2+}$  by the endoplasmic reticulum, and inhibition of voltage-dependent  $\text{Ca}^{2+}$  channels, blocking the  $\text{Ca}^{2+}$  influx <sup>25</sup>. Both, cGMP and cAMP levels are modulated by phosphodiesterase (PDE) enzymes, which cleave these signaling molecules to 5'GMP and 5'AMP, respectively (Figure 3). Phosphodiesterase-5 (PDE-5) is a key enzyme in the NO/cGMP signal transduction pathway and functions to restrain smooth muscle cells relaxation and erectile process <sup>18</sup>. Predominantly expressed in CC, PDE-5 catalyzes the hydrolysis cGMP to the inactive metabolite 5'GMP. Nowadays, the PDE5 inhibitors are the first-line treatment for ED <sup>26</sup>.

Another mechanism which has been demonstrated to be involved in maintenance of the erectile process is the phosphatidylinositol 3-kinase (PI3-kinase) pathway that activates the serine/threonine protein kinase Akt (also known as PKB). It causes direct phosphorylation of eNOS, reducing the enzyme's calcium requirement and causing increased production of NO. It has been suggested that rapid, brief activation of nNOS initiates the erectile process, whereas PI<sub>3</sub>-kinase/Akt-dependent phosphorylation and activation of eNOS by augmented

blood flow and endothelial shear stress lead to sustained NO production and maximal erection<sup>27</sup>.

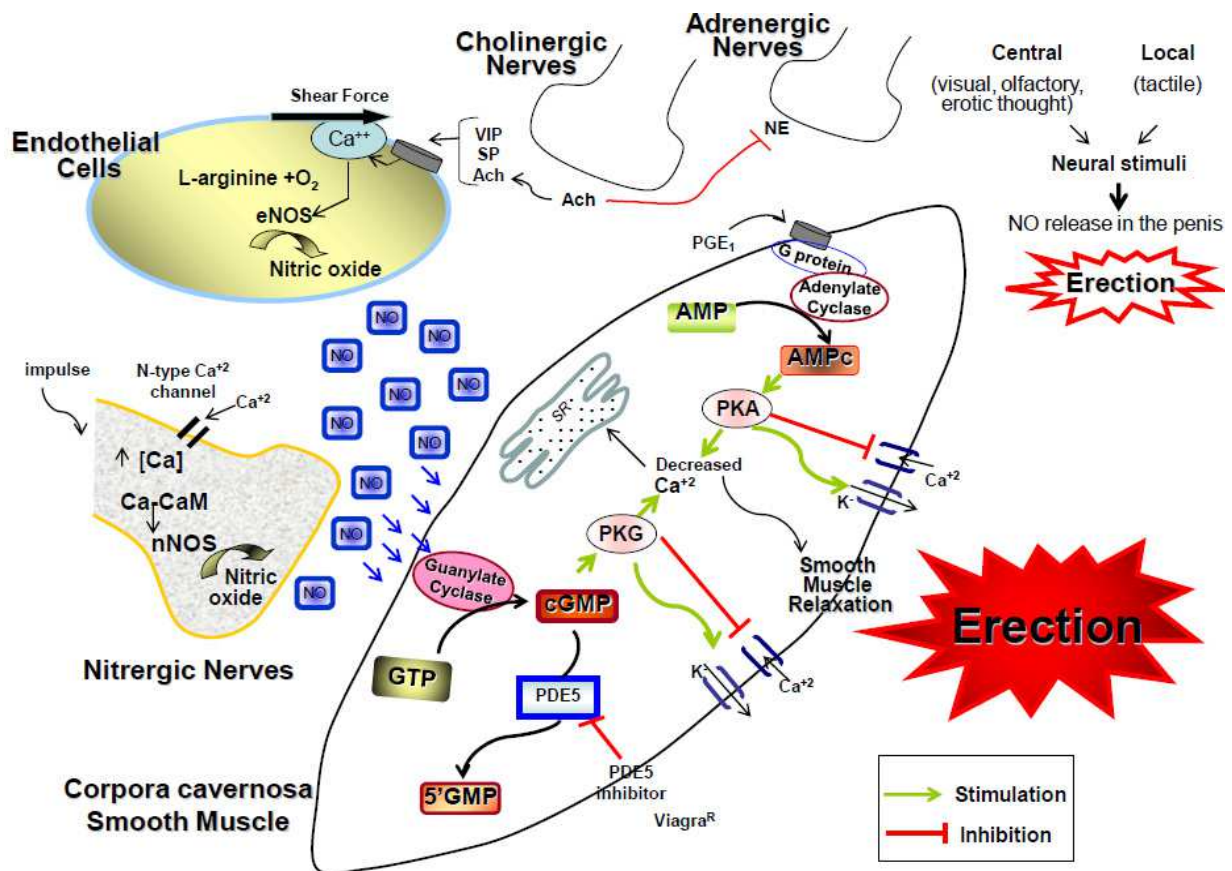


Fig. 3. Regulation of cavernosal smooth muscle relaxation by NO released from the nitrenergic nerve and sinusoidal endothelium. Central and/or local excitation evoke stimulation of the endothelial cells and nitrenergic nerves in the penis, causing  $Ca^{2+}$  influxes which promote eNOS and nNOS activation, increasing NO production. NO binds to soluble guanylate cyclase (GC) inside cavernous muscle smooth catalyzing the conversion of GTP in cyclic GMP (cGMP). AMPc and high levels of cGMP result in vasodilatation of arteries and sinusoidal spaces of the corpus cavernosum, by decreasing intracellular calcium concentration, which is due to activation of PKA and PKG, leading consequently to erection. In addition, PKA and PKG cause inhibition of calcium channels and activation of potassium channels. Abbreviations: CaM, calmodulin; nNOS, neuronal nitric oxide synthase; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate; GMP, guanosine monophosphate; cGMP, cyclic GMP; PDE5, phosphodiesterase type 5; PKG, protein kinase G; PKA, protein kinase A.

### 3.2 Flaccidity and detumescence

Rich adrenergic innervation found in the penis, mainly surrounding the cavernosal arteries, and norepinephrine has been suggested as the chief neurotransmitter derived from the sympathetic nervous system to control flaccidity and detumescence<sup>8, 28</sup>. Also, the penis is kept in the flaccid state due to endothelins. Penile smooth muscle cells not only respond to, but also synthesize, endothelin-1 (ET-1)<sup>29</sup>. Vasoconstriction in erectile tissue induced by ET-1

appears to be predominantly mediated by  $ET_A$  receptor. In the penis, ET-1/ $ET_A$  receptor-mediated biological effects involve activation of the inositol trisphosphate ( $IP_3$ )/calcium ( $Ca^{2+}$ ) and RhoA/Rho-kinase signaling pathways<sup>30</sup>. However, both  $ET_A$  and  $ET_B$  receptors have been found in human CC smooth muscle membranes, and it cannot be excluded that both receptor subtypes are functional<sup>28</sup>. The role of  $ET_B$  receptors in the CC has not been clarified. This receptor activation is known to possibly induce a NO-mediated decrease in penile vascular tone<sup>31</sup>.

The intracellular mechanism in the absence of arousal stimuli, initiates with activation of G proteins following ligand binding to membrane receptors in order to keep cavernosal arterioles and sinuses constricted, maintaining the penis in the non-erect state. Subsequently to G protein activation, two signaling pathways are brought into play to cause smooth muscle contraction in the arterioles and cavernosum: the well characterized  $Ca^{2+}$  dependent pathway (phospholipase C) and the recently identified RhoA/Rho-kinase pathway known as  $Ca^{2+}$  sensitization. The Rho-kinase pathway is intrinsically involved with the process of smooth muscle contraction. The  $Ca^{2+}$  sensitivity of smooth muscle reflects the ratio of activities of MLCP to myosin light-chain kinase (MLCK), resulting in contraction or relaxation. Activation of G-protein coupled receptors by several agonists such as endothelin, angiotensin II, and noradrenalin, leads to the exchange of GDP for GTP on the small monomeric GTPase RhoA. This event activates RhoA and is catalyzed by the guanine nucleotide exchange factors, which causes dissociation of RhoA from its binding partner, Rho-guanine dissociation inhibitor. As a result, RhoA translocates from the cytosol to the membrane, allowing the downstream activation of several effectors such as Rho-kinase. Phosphorylation of the regulatory subunit of MLC phosphatase by Rho kinase causes inhibition of phosphatase activity, which increases the contractile response at a constant intracellular calcium concentration<sup>32</sup>. It is now widely accepted that MLCK and the RhoA/Rho-kinase pathway are two major cellular targets for regulating  $Ca^{2+}$  sensitivity of myosin light chain, and they generally operate in parallel. RhoA/Rho-kinase activity is a fundamental component to keep the penis in the non-erect state, and this pathway is upregulated in ED. Also, the essential balance between contraction and relaxation in the penis, which is maintained by the RhoA/Rho-kinase and NO/cyclicGMP pathways, is modified in this pathology<sup>33-34</sup>. It has been demonstrated that Rho-kinase antagonism stimulated rat penile erection independently of NO suggesting that this principle could be a potential alternative for ED treatment<sup>35-36</sup>. Many studies have suggested that NO inhibits RhoA/Rho-kinase activity<sup>37-38</sup>. Increased RhoA/Rho-kinase activity may lead to abnormal contractility of the CC and has been suggested to be involved not only in ED, but in several diseases which are risk factors for ED such as hypertension and diabetes<sup>39</sup>.

Another mechanism involved in penile vasoconstriction in absence of arousal stimuli, is the phospholipase C (PLC) pathway. The stimulation of PLC occurs through the binding of vasoconstrictor agonists, such as norepinephrine (NE), angiotensin II (Ang II), endothelin-1 (ET-1) and others, to their respective receptors. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate ( $PIP_2$ ) to release  $IP_3$  (inositol 1,4,5-trisphosphate) and DAG (1,2-diacylglycerol).  $IP_3$  binds to specific receptors ( $IP_3R$ ) on the endoplasmic reticulum (ER) to stimulate the release of  $Ca^{2+}$  from the intracellular stores. DAG directly stimulates protein kinase C (PKC), which can regulate smooth muscle tone by controlling ion channels, allowing  $Ca^{2+}$  influx. PKC also phosphorylates multiple substrates to facilitate contraction (figure 4).



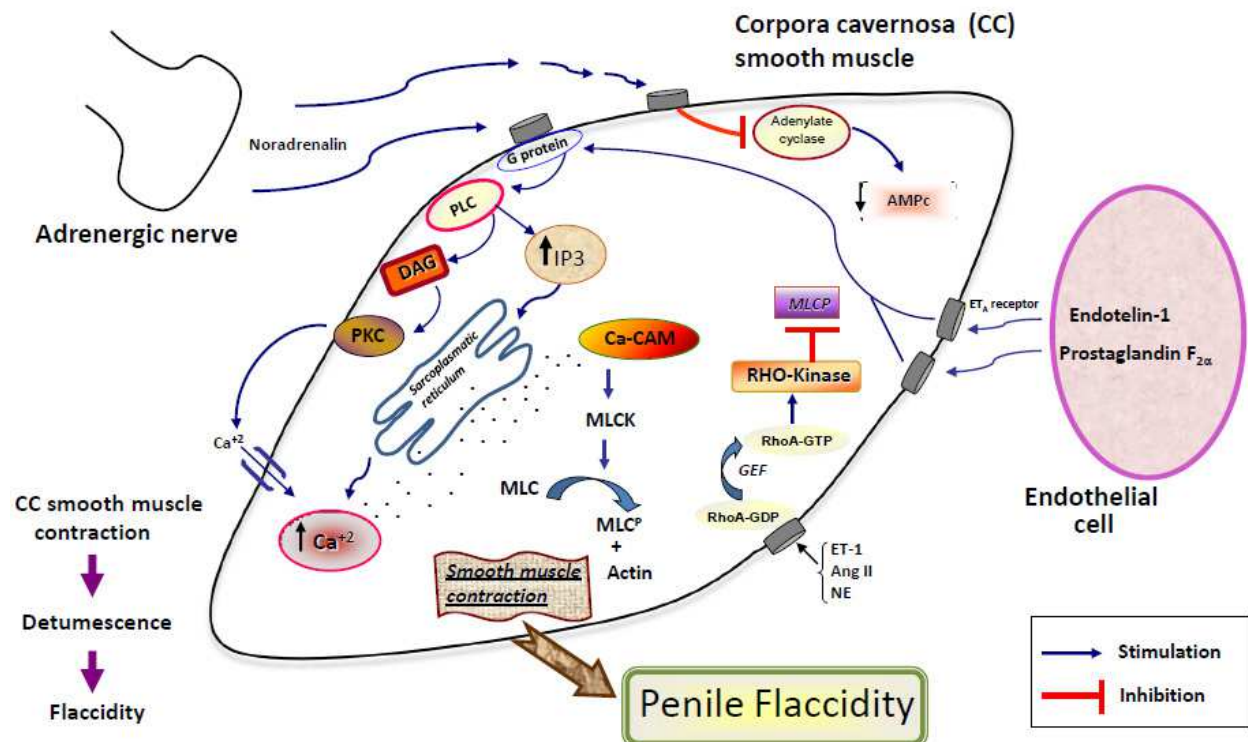


Fig. 4. Regulation of cavernosal smooth muscle contraction leading to penile flaccidity. Pathways mediating the contraction of smooth muscle in CC, which is regulated by an increase in cytosolic Ca<sup>2+</sup>, are illustrated.

#### 4. Emergent mechanisms associated with ED

Various aspects of neurotransmission, impulse propagation, and intracellular transduction of signals in penile smooth muscle remain to be elucidated. Nevertheless, the information about mechanisms involved in erection is quickly increasing and details regarding new pathways are constantly being added. The renin-angiotensin system (RAS), TNF- $\alpha$ , MAP Kinases and arginase II are some of the new insights in this field.

##### 4.1 Renin-angiotensin system

In the past decade, it has become apparent that the renin-angiotensin system (RAS) is involved in the regulation of ED. There is evidence that the local RAS exists within the CC<sup>40</sup> and that several active peptides, particularly angiotensin II (Ang II), may be involved in the erectile mechanism. Ang II is the main effector of RAS that regulates important physiologic functions. The conventional idea of RAS as a systemic system has been extended recently. Many organs and tissues have components of RAS, working in a paracrine manner<sup>41</sup>. Tissue RAS synthesizes Ang II locally and is modulated independently of systemic RAS. It has been demonstrated that Ang II activates the RhoA/Rho-kinase pathway via AT<sub>1</sub> receptor, which is dominantly expressed in the smooth muscle and endothelial cells of the blood vessel wall, leading to the inhibition of myosin light chain phosphatase (MLCP)<sup>42-43</sup>. Another significant function of AT<sub>1</sub> is to activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increasing reactive oxygen species (ROS) production. ROS rapidly react with NO, reducing its bioavailability, and also stimulate RhoA/Rho-kinase



activity<sup>44-45</sup>. Additionally, both Ang II<sup>46</sup> and AT<sub>1</sub><sup>47</sup> were detected in endothelial and smooth muscle cells from CC, and comparing the different stages of penile flaccidity, tumescence, rigidity, and detumescence, Ang II levels were significantly higher during detumescence<sup>47</sup>. Human CC produces and secretes physiological amounts of Ang II, as much as 200-fold greater than that in plasma<sup>46</sup>. Furthermore, *in vivo* experiments demonstrated that injection of Ang II into the CC terminated spontaneous erections observed in anesthetized dogs<sup>46</sup>. Chronic infusion of exogenous Ang II for 4 weeks induced ED in Sprague-Dawley rats<sup>48</sup>. It seems that RAS is crucial in ED<sup>49</sup>.

Reinforcing the association of RAS and ED, angiotensin-converting enzyme (ACE) has been found in the endothelial cells of dog CC<sup>50</sup>, and ACE mRNA expression is up-regulated in a rat model of arteriogenic ED, although it is expressed at very low levels in the penis of control rat<sup>51</sup>. Results from human CC smooth muscle showed that Ang II and NO interact to modulate penile function, since an AT<sub>1</sub> antagonist potentiated sodium nitroprusside (a NO donor) and electrical field stimulation mediated CC relaxation. Also, the authors suggested that Ang II response involves the production of superoxide and the development of oxidative stress<sup>52</sup>. Taken together, evidence from many studies suggests that the main function of the RAS system is Ang II-mediated contraction, contributing to maintenance of the penis in a flaccid state. However, the RAS system consists of two major arms: a vasoconstrictor/proliferative arm in which the major mediator is Ang II acting on AT<sub>1</sub> receptors, and a vasodilator/antiproliferative arm in which the main effector is Ang-(1-7) acting via G protein-coupled receptors Mas<sup>53</sup>. The Ang-(1-7)-Mas axis may play an important role in penile erection. This receptor has been observed in rat CC, and it has been demonstrated that Ang-(1-7) acts as a mediator of penile erection by activation of Mas and subsequent NO release. Additionally, in the absence of Mas erectile function was severely compromised<sup>54</sup>.

#### 4.2 TNF- $\alpha$

The emerging role for tumor necrosis factor-alpha (TNF- $\alpha$ ) in ED has been discussed. It is a pro-inflammatory cytokine originally defined by its antitumoral activity and is involved in many cardiovascular diseases (CVD), including heart-failure and atherosclerosis<sup>55-56</sup>. In these diseases, TNF- $\alpha$  plasma levels are significantly increased and the vascular endothelium is the major target for the actions of TNF- $\alpha$ . *In vivo* administration of this cytokine induces impairment of endothelium-dependent relaxation in a diversity of vascular beds and decreases the release of NO<sup>57</sup>. Endothelium dysfunction is a key event in the pathophysiology of ED and, importantly, endothelium dysfunction is impaired in the presence of increased oxidative stress and inflammatory conditions<sup>55</sup>. A low-grade inflammatory process is associated with several CVD, and accordingly, cytokines levels, including TNF- $\alpha$ , are increased in response to inflammation and contribute to the changes in vascular reactivity observed in these conditions<sup>58-59</sup>. TNF- $\alpha$  has been described as an important contributor to many cardiovascular disorders<sup>55</sup>. Patients with ED present increased expression and elevated plasma levels of inflammatory markers and mediators among them TNF- $\alpha$ <sup>60</sup>, which have been also observed in patients with hypertension. An emerging basic science and clinical data base provides a strong argument for endothelial and smooth muscle dysfunction as a central etiologic factor in systemic and peripheral vascular diseases, such as ED. It has been raising the idea of ED as an early sign of CVD<sup>61</sup>. Once CVD appears right after ED and after the levels of TNF- $\alpha$  start to increase<sup>62-63</sup>, seems

that this cytokine may represent not only a common point between ED and CVD, but its increasing levels associated with ED may be a predictor of cardiovascular events<sup>64</sup>.

TNF- $\alpha$  has been associated with Rho-kinase signaling in endothelial cells. This cytokine not only induces inflammatory gene transcription, but also activation of RhoA and Rho-kinase<sup>65</sup>. In addition, TNF- $\alpha$  leads to increased Ca<sup>+2</sup> sensitivity via activation of the RhoA/ROCK pathway, a mechanism that may contribute not only to TNF- $\alpha$ -induced airway hyperresponsiveness and hyperreactivity<sup>66-67</sup>. It was recently demonstrated that TNF- $\alpha$  KO mice shown increased number of spontaneous erections, also these animals have enhanced nNOS expression in CC tissue<sup>68</sup>, which suggests that TNF- $\alpha$  down regulates nNOS expression in this tissue<sup>68</sup>. In another work, the same authors showed that TNF- $\alpha$ -infused mice displays decreased NANC-dependent relaxation and increased sympathetic-mediated concentrations *in vivo*, which would contribute to penile detumescence to occur<sup>69</sup>. Enhanced direct adrenergic responses were also observed in CC tissue from these animals, and it was suggested that downregulation of eNOS and nNOS may be the mechanism underlying the functional modifications in CC strips from TNF- $\alpha$  infused mice<sup>69</sup>. Endothelin-1 not only induces vasoconstriction, but it also stimulates the expression of adhesion molecules and activates transcriptional factors responsible for the coordinated increase in the expression of many cytokines and enzymes, which can in turn lead to the production of inflammatory mediators<sup>70</sup>. Additionally, RAS system and Ang II, the main known mediator of RAS, induces vascular injury through many mechanisms, including vasoconstriction, oxidative stress and inflammation. Both peptides have been shown to increase TNF- $\alpha$  levels and this pro-inflammatory cytokine also positively regulates release of these vasoactive peptides<sup>71-72</sup>. Finally, sexual performance has been negatively associated with circulating levels of endothelial inflammatory parameters<sup>73</sup>. Further studies are necessary to better clarify the role of TNF- $\alpha$  in ED and its mechanism in CC dysfunction. The positive point is that now we have access to target anti-TNF- $\alpha$  a therapy.

### 4.3 Arginase

The involvement of arginase in ED has been evident in recent years. Arginase catalyses the conversion of L-arginine to ornithine plus urea. Arginase exists in two isoforms, the hepatic type, arginase I and the extrahepatic type, arginase II<sup>74</sup>. Both isoforms are expressed in human CC tissue<sup>75</sup>, but it seems that arginase II is the predominant isoform involved in ED mainly when this condition is associated with age and diabetes<sup>76-77</sup>. In mammalian cells, L-arginine is used as a substrate by both NOS and arginase. NO is derived from L-arginine by nitric oxide synthase (NOS) and both endothelial (eNOS) and neuronal (nNOS) isoforms of the CC serve as sources to generate essential levels of NO. NO production depends on NOS activity and NOS protein expression. On the other hand, NO production absolutely depends on the availability of L-arginine to NOS, since NOS shares L-arginine as a common substrate with arginase<sup>78</sup>. Considering this, L-arginine catabolism via the arginase pathway can act as an endogenous negative control system to regulate overall NO production. ED mechanisms involve oxidative stress and vascular inflammation<sup>79</sup>, both of which have been associated with enhanced arginase activity and expression in the vasculature<sup>77</sup>. Recently, it has been demonstrated that diabetes-induced ED involves elevated arginase activity and expression<sup>80</sup>. Also, previous studies suggest that arginase activity in the CC is increased by hyperglycemia and aging<sup>81</sup>.

Aging-associated ED involves abnormalities at multiple levels of the NO/cGMP signaling in the penis. These include reduced NANC nerve fibers in CC, decreased constitutive NOS activity, impaired endothelium-dependent smooth muscle relaxation and reduced NO bioavailability<sup>82-83</sup>. It has been observed that dietary L-arginine supplementation as well as acute infusion of L-arginine results in improved NO release and increased endothelium-dependent vasodilatation in the penis<sup>84</sup>. The basis by which L-arginine supplementation can improve the endothelial function and NO release is questionable. Studies have been shown that eNOS expression is upregulated with advanced age in the penis and in peripheral vasculature. However, eNOS activity is reduced such that, for any given concentration of L-arginine, vascular production of NO is reduced<sup>85-86</sup>. Nowadays, we have evidence of a biological role of arginase in regulating erectile function in the aged penile vascular bed at both the molecular and functional level. It has been demonstrated that penile endothelial cells isolated from the aged mouse penis overexpressed arginase and, as a result, decreased eNOS activity and impaired vascular function. Moreover, inhibition of arginase via an adeno-associated virus (AVV) gene transfer of anti-arginase in this tissue increases penile eNOS activity and cGMP levels, thus restoring endothelial-derived NO vasodilatation and erectile function<sup>79</sup>, speculating that an antisense for arginase may represent a novel molecular therapeutic target for the treatment of age-associated vasculogenic ED. Regarding diabetes-associated ED, reduced nitric and endothelial dependent smooth muscle relaxation, as well as arginase activation and diminished NO production are involved<sup>87-88</sup>. In addition, it has been well documented that a major causative factor contributing to ED in diabetic patients is the reduction in the amount of NO synthesis in CC. Recently, it was demonstrated that arginase II deletion prevents diabetes-impairment in CC relaxation<sup>80</sup>. Since a specific arginase inhibitor is not available, in this study they used diabetic arginase II knockout mice. These animals did not exhibit increased arginase activity and expression, as well as decreased nNOS and phospho-eNOS (at Ser-1177 and Thr-495) levels. Arginase has been involved in sexual disorders not only in men, but also in women. Administration of arginase inhibitors *in vitro* and *in vivo* enhances engorgement in male and female genitalia<sup>89</sup>. There is no doubt that arginase is involved in ED. However, more complete understanding about the exact mechanism leading to disruption of erectile dynamic by arginase is necessary, as well as further research.

#### 4.4 MAP-Kinases

Mitogen-activated protein kinases (MAPK) are a group of serine/threonine protein kinases which play an important role in cellular process, such as proliferation, stress response apoptosis and immune defense<sup>90</sup>. The extracellular-signal-regulated kinase 1/2 (ERK1/2), p38 MAPK and the JUN N-terminal kinase (JNK) are the three most defined MAPK pathways<sup>91</sup>. Not long ago, evidence of involvement of ERK1/2 and p38 MAPK in the ED began. It seems that these MAPKs are indirectly associated with NOS regulation, which affects NO availability. It has been observed that ERK plays a key role in eNOS regulation<sup>92</sup>. In addition, phosphorylation of eNOS catalysed by ERK can lead to enzyme inhibition, and it was shown that *in vivo* phosphorylation of eNOS by ERK is associated with a reduction in enzyme activity. ERK inhibits eNOS by phosphorylating the enzyme in endothelial cells<sup>92</sup>. ERK has been involved in various pathological conditions; one major mechanism involved in the regulation of inflammatory processes is the activation of ERK<sup>93</sup>. Regarding cavernosal tissue, an inhibitory influence on activity of eNOS by ERK has been described in humans<sup>94</sup>.

The first study showing a link between ERK1/2 and the CC was published in 2002 and the authors demonstrated that this kinase is present and active in human CC. Also, they found that the endothelial expression of ERK was more pronounced than muscular expression, and tissue from patients with ED showed a higher expression of the active ERK<sup>94</sup>. ERK can be triggered by cellular stresses such as oxidative stress and hyperglycemia, which play an important role in the development of diabetic complications<sup>95</sup>, a disease associated with ED. Recently, it was demonstrated that ERK inhibition decreases arginase activity and improves CC relaxation in streptozotocin (STZ)-induced diabetic mice (Nunes, 2011). Hyperglycemia in STZ-induced diabetic mice stimulates adipogenic induction of lipid accumulation and

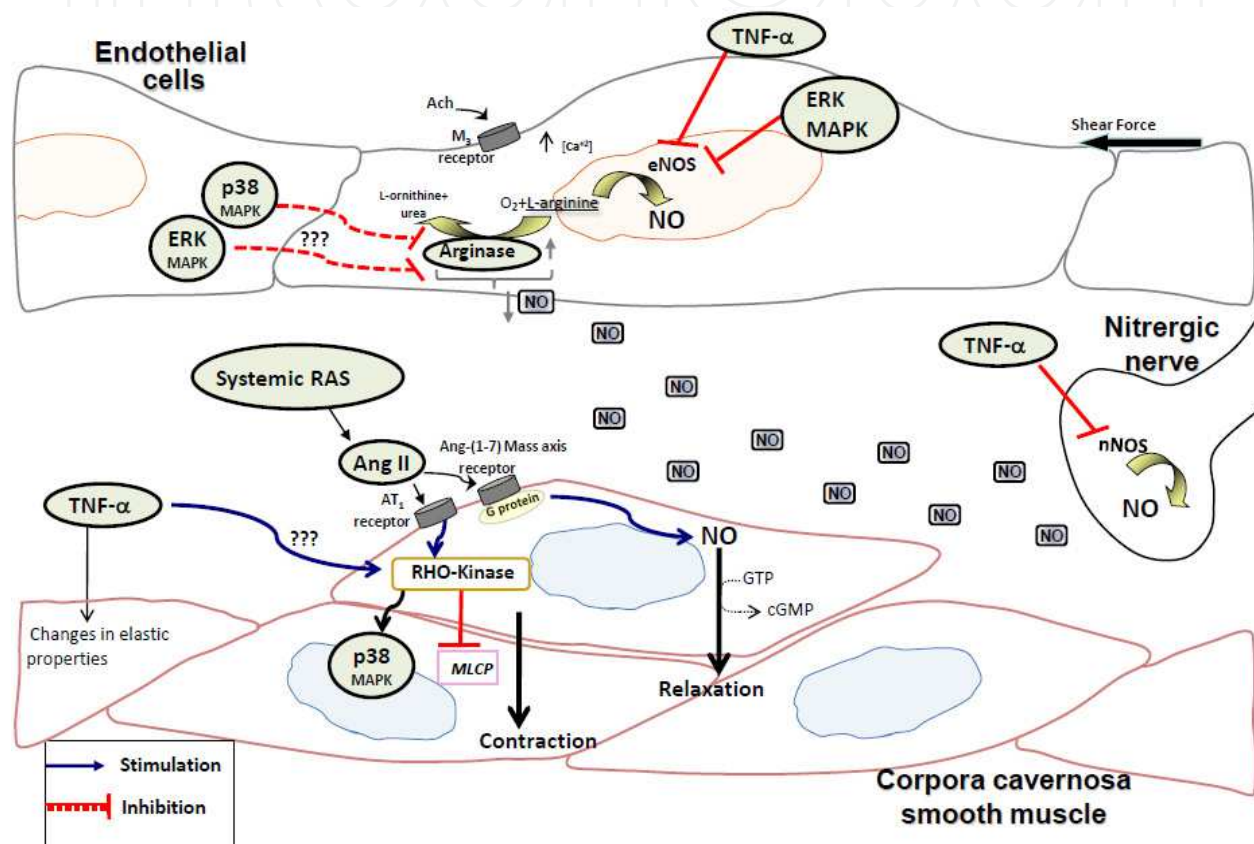


Fig. 5. Emergent pathways involved in ED. The influence of renin-angiotensin system (RAS), TNF- $\alpha$ , ERK and P38 MAPK, and Arginase II in ED are illustrated. Tissue RAS synthesizes Ang II locally, which acts via two different receptors: AT-1, leading to activation of RHO-kinase and consequently MLCP inhibition, contributing to penile flaccid, or Ang-1-7 Mass axis G-protein coupled receptor evoking NO release and facilitating CC relaxation. Additionally, Ang II can activate p38, which is involved in NOS regulation. TNF- $\alpha$  promotes downregulation of eNOS and nNOS, contributing to ED. In addition, TNF- $\alpha$  may lead to increased Ca<sup>2+</sup> sensitivity, via activation of the RhoA/ROCK pathway, (???) in the penis. Since arginase and eNOS share L-arginine as a common substrate, increased arginase activity can limit NO availability, making the erectile function difficult. ERK and p38 MAPKs are indirectly associated with NOS regulation, which affects NO availability. Inhibitors for ERK and p38 in CC tissue resulted in decreased arginase activity, suggesting an association between these kinases and arginase. However, this mechanism in ED still needs to be clarified.



involves ERK signaling pathway <sup>96</sup>. Also, neuropathy is a common complication of long-term diabetes <sup>97</sup>. Accordingly, the recent study showed that diabetes increased expression of activated ERK and arginase activity in CC and this effect was blocked by acute treatment with PD98059 (an ERK inhibitor). Also, the impaired cavernosal relaxation from STZ-diabetic mice was attenuated by treatment with an ERK inhibitor, observed in nitrenergic and endothelium-dependent relaxation responses. The authors suggested that ERK inhibition prevents the elevation of penile arginase activity and protects against ED caused by diabetes <sup>98</sup>. However, the mechanism involving ERK and arginase in ED is unclear and needs to be better understood.

There are a few studies associating ERK and P38 MAPK with ED. RhoA/Rho-kinase has been indicated as an upstream regulator of MAPK family members such as p38 MAPK <sup>99</sup>. Increased p38 MAPK in response to stress stimuli, including hyperglycemia, contributes to diabetic somatic neuropathy <sup>100</sup>. The first study connecting ED and p38 demonstrated that inhibition of p38 MAPK corrects nitrenergic neurovascular function in diabetic mice CC <sup>101</sup>. It has been described that Ang II markedly activates p38 MAPK <sup>102-103</sup> and inhibition of p38 MAPK attenuates organ damage and improves vascular function in cardiovascular diseases <sup>104-105</sup>. Recently, it was demonstrated that p38 MAPK increases arginase activity and contributes to endothelial dysfunction in CC <sup>106</sup>. This study showed that acute treatment with p38 inhibitor prevents increased arginase activity and expression of phosphorylated p38 MAPK levels in CC from mice treated with Ang II. Also, decreased eNOS phosphorylation at Ser-1177 due to Ang II treatment, was prevented. <sup>106</sup>. Although further research is needed to better clarify the exact role of these kinases in ED, new insights pointed to these pathways as a new therapeutic target worthy of consideration for clinical trials.

## 5. Endothelial dysfunction in vasculogenic ED

A number of both clinical and preclinical studies on hypercholesterolemia, hypertension, diabetes, and aging have demonstrated endothelial dysfunction to be a critical factor in the development of vasculogenic ED <sup>107</sup>. Since the erectile function is a mechanism which requires a sensitive balance between the vasodilators and vasoconstrictors agents, any modification or impairment in endothelial function contributes to ED. Nowadays, because a systemic endothelial may functionally manifest itself early in the penile endothelium, the possibility arises that ED may be an early indicator of cardiovascular diseases <sup>61, 108-110</sup>. In addition, since the penis is a rich vascularized organ, penile erection is, in large part, a vascular event. The endothelium, which is a layer of epithelial cells that lines structures of the cardiovascular system, is pivotal to the regulation of vasomotor tone. Impaired vasodilatation is closely linked with endothelial dysfunction, and endothelial cells are the primary source of NO, which is a crucial vasodilatory neurotransmitter involved in the regulation of vascular wall function, specifically in the penis <sup>19</sup>. At the cellular level, endothelial dysfunction results in impaired release of NO. Oxidative stress, which is directly toxic to the endothelium and also interferes with NO signaling, is a strong factor responsible for the endothelial dysfunction in ED. In addition, free radical damage and impaired function, as well as NO availability, also results in increased adhesion and aggregation of platelets and neutrophils, and the release of vasoconstrictor substances <sup>111-112</sup>. Since the penis is a vascular organ, it may be very sensitive to changes in oxidative stress and systemic

levels of NO for many reasons. The small diameter of the cavernosal arteries and the eminent amount of endothelium and smooth muscle (per gram of tissue compared to other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease <sup>61</sup>.

Oxidative stress has been implicated in endothelial damage or destruction of NO <sup>113</sup> as previously mentioned. It occurs when cells are exposed to excessive levels of reactive oxygen species (ROS) as a result of an imbalance between pro-oxidants and the protective mechanisms conferred by antioxidants <sup>114</sup>. ROS is a superoxide ( $O_2^-$ ) which interacts with NO reducing NO bioavailability and resulting peroxynitrite (ONOO<sup>-</sup>) formation. It has been demonstrated that the blockade of NOS increased basal superoxide production in penile arteries, suggesting that the release of ROS is modulated by its interaction with endogenous endothelial-derived NO, probably by producing peroxynitrite that reduces the bioavailability of both radicals <sup>115</sup>. In addition, peroxynitrite and superoxide have been reported to increase the incidence of apoptosis in the endothelium of cavernosal smooth muscle, resulting in denudation of endothelium and further reduction of available NO <sup>116</sup>. NOS, enzyme responsible for NO generation, uses L-arginine as a substrate and promotes its oxidation with NADPH and  $O_2$  consumption to yield citrulline and NO. NADPH oxidase is a big source of superoxide radicals and many authors have reported that up regulation of this enzyme is associated with an increased risk of vascular diseases <sup>117</sup>. Also, superoxide anions plays a role in natural aging process and the prevalence and severity of ED increase with age.

Another mechanism associated endothelial damage and ED is the recently identified advanced glycation end products (AGEs). It is believed that when AGEs are increased, NO cannot interact with GS, resulting in decreased CGMP levels and ultimately functional ED. Recently, it has been demonstrated that inhibitors of AGE formation can prevent formation of a range of complications in experimental diabetic animals, including ED <sup>118-119</sup>. AGEs are elevated in diabetic human penile tissue and it has been localized to the collagen of the penile tunica and corpus cavernosum <sup>120</sup>. Furthermore, AGEs and their receptors have been described to elevate the activity of endothelin-1, a vasoconstrictor, in rat corpus cavernosum <sup>121</sup>, and AGEs production is associated with increased superoxide anion. O-linked N-acetylglucosamine (O-GlcNAc) is the major AGE product implicated in cavernosal dysfunction in diabetic patients. It has been reported a significant increase in the O-GlcNAc modification of eNOS and reduced phosphorylation of eNOS at baseline and following electrical stimulation in cavernosal tissue from diabetic rats compared with the controls <sup>122</sup>. Finally, increased AGEs has been reported in penile tissue from aged man <sup>123</sup>.

Although the vascular endothelium is capable of self-repairing in general, any disruption in the penile endothelium balance may affect the dynamic of erectile function since the intact endothelium is critical to normal erection. Increase production of ROS has been associated with decreased normal erectile response, mainly because the reduction in NO availability, which is also observed due to endothelium damage <sup>113</sup>. Consequently, ED can be the result of any number of structural or functional abnormalities in the penile vascular bed. Accordingly, ED may result from occlusion of the cavernosal arteries by atherosclerosis (structural vascular ED), impairment of endothelial dependent and/or independent smooth muscle relaxation (functional vascular ED), or a combination of these factors. Thus, it seems that endothelial dysfunction is sometimes a primary factor involved in ED even though reduced NO from NANC nerves has a significant contribution in ED.

## 6. Conclusion

The molecular and clinical understanding of ED continues to gain ground at a particularly fast rate. Significant scientific advances during the last 2 decades have increased our knowledge regarding physiology and pathophysiology of penile erection. Different parts of the pathways involving ED have been studied intensely and the investigations of new components in this mechanism are emerging. The main target in the mechanism associated with ED is still NO, and the deep understanding of NO/cGMP signaling has supported, not only the molecular understanding of the tumescence, but also added significantly in the treatment of the ED, including the possibility of stem cell use and gene therapy. Also, the new components found to be involved in ED may be a potential target for development of novel drugs. However, the erectile mechanism is not completely elucidated and despite the efficacy of current therapies, current knowledge remains insufficient to address a growing patient population who do not respond to conventional treatment.

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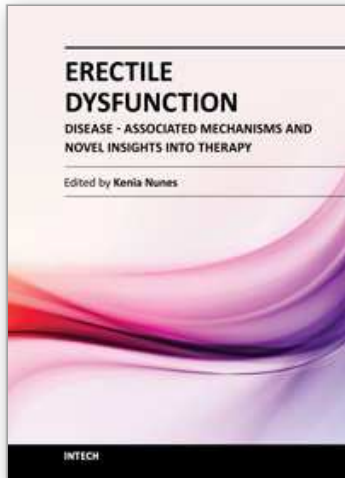
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## **Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy**

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Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

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