Chapter 7

Nitric Oxide Synthase in Male Urological and Andrologic Functions

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Additional information is available at the end of the chapter

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Abstract

Nitric oxide (NO), a crucial signaling molecule, is synthesized by the nitric oxide synthase (NOS) enzyme. The significant effects of NOS are under exploration, and the roles of potential therapy targets for diseases of NOS are widely accepted. In this chapter, we summarized the important roles of NOS mainly on pathogenesis of prostate diseases, male infertility, erectile dysfunction and, addition, the potential therapeutic efficacies of NOS for those diseases.

Keywords: nitric oxide synthase, nitric oxide, prostate cancer, male infertility, erectile dysfunction, male reproduction

1. Introduction

Urology and andrology are the branches of medicine that focus on urinary tract system and male reproductive organs. In recent years, incidences of diseases in urology and andrology system such as prostate cancer and male infertility are increasing and causing heavy burden to our society. Growing studies have been demonstrating that nitric oxide synthase (NOS), which synthesized nitric oxide (NO) by converting L-arginine to L-citrulline, locates in tissues of urinary and male reproductive system and acts as key regulators for sexual function, male reproduction, cancer progression and so on [1–3]. The aims of this chapter are to present the roles of NOS and the recent advances of regulation and therapy function with regard to sexual function, male infertility, prostate carcinoma, Peyronie disease, priapism and cryptorchidism.

2. NOS and male sexual function

2.1. NOS and erectile dysfunction

Erectile dysfunction (ED) refers to the symptom that the penis cannot reach and (or) maintain the adequate erection to complete the satisfaction of sexual intercourse, and the course of disease will last at least 6 months or more. Penile erection is an integrated process of artery blood supply and cavernous blood storage launched by nerve, and during this process, neurotransmitter plays an important role [4]. NO is a main messenger, which involves in the induction and maintenance of erection through hemangiectasis and corpus cavernosum relaxation [5]. It has been clear that NO penetrates the smooth muscle cell membrane and catalyzes the formation of cGMP after combining with the ornithine enzyme on the iron ring and then changing the intracellular calcium concentration of smooth muscle to cause relaxation.

2.1.1. NOS in penile tissue

The nNOS and iNOS were found in the central nervous system, especially the hypothalamic area, such as paraventricular nucleus and the medial optic zone, that control the erectile and sexual behavior and also regulate penile erection through spinal nerve centers [6, 7] (**Figure 1**). Specially, nNOS mainly distributes in the penile and pelvic nerve plexus in adult rats, whereas eNOS is in the penis and pelvic area of the urethra but less in the body part of the penis [8, 9].

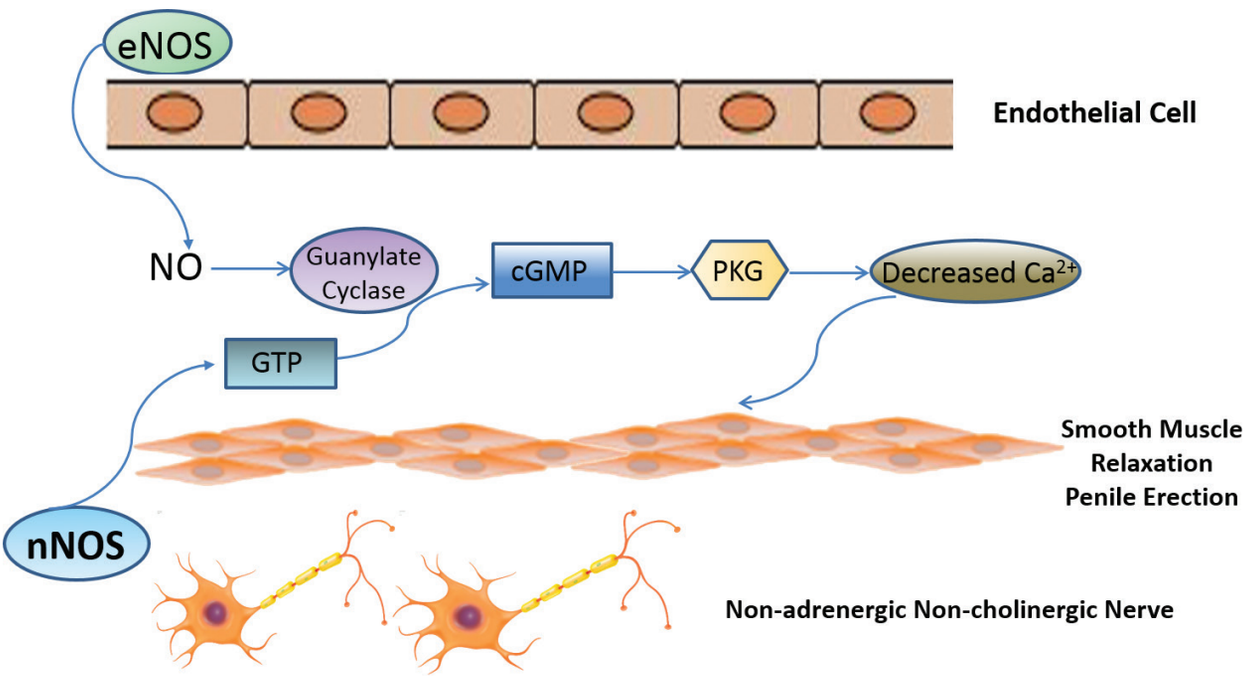

Figure 1. Role of NOS and NO in penile erection. The nNOS and iNOS regulate penile erection through NO/cGMP/PKG pathway. Abbreviations: eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G.

2.1.2. Current reviews on the effects of NOS on disease-related ED

2.1.2.1. Diabetes-related ED

A possible percentage ranges from 50% to 90% of diabetes patients suffer from ED [10], which counts around three times more than that in healthy cohort. Also, previous report showed that diabetes patients who firstly suffered from ED had a younger age in average compared with people without diabetes and more severe appeared of their symptoms [11]. It has now reached a consensus on the relationship between diabetes and ED, the damage of endothelial cell, ultrastructure changes in cavernous smooth muscle and matrix fibrosis are the common factors affecting the cavernous diastolic function and resulting in ED [12], and damage of eNOS-NO-cGMP pathway was considered to be the main molecular mechanism [13]. The expression of Recombinant Nitric Oxide Synthase Trafficker (NOSTRIN) in Dulbecco's modified eagle medium (DMED) corpus cavernosum increased while the expression of eNOS decreased. It is theorized that increased NOSTRIN may be an important mechanism for the reduction of eNOS expression, while further study is still needed [14].

2.1.2.2. Benign prostatic hyperplasia-related ED

Approximately 49% of BPH patients suffer from ED. A significant correlation was reported between BPH/lower urinary tract obstruction (LUTS) and ED after excluding the effects of age and other etiologies on ED [15, 16]. BPH/LUTS seems to be one of the most harmful factors contribute to ED compared with diabetes, hypertension and (or) heart disease [17]. In fact, both parasympathetic innervation of prostate and cavernous nerve of penis are from the pelvic plexus [18]. Pathophysiology studies also showed that the mechanisms of BPH are similar to those of sexual dysfunction which include decrease of the ratio of endothelial NOS/NO, enhancement of endothelial presenilin-1 contraction effect, overreaction of autonomic nervous of bladder, prostate and penis, enhancement of signaling pathway Rho kinase expression/activity and (or) pelvic vascular sclerosis [19]. Since NOS has been found to play significant effects on BPH patients with ED, new treatment by exogenous NO donor and NOS activating enzyme would be promising [20]. However, only few animal experiments have been under exploration up to date, and the mechanisms for the occurrence of ED in BPH patients are still needed to be identified.

2.1.2.3. Hypertension-related ED

Hypertension is another important risk factor for ED. Jensen et al. reported that nearly 27% of hypertensive patients suffered from ED [21]. The increase of plasma asymmetrical dimethylarginine (ADMA) concentration caused reduction of the NO expression in penile tissue by inhibiting the NOS activity, which might be a possible mechanism for hypertension-related ED [22].

2.1.3. Possible therapy strategies of NOS on ED

Increasing evidence has been indicating that L-Arg-NO-cGMP pathway might be a crucial mechanism of penile erection [23]. As a key enzyme in the synthesis of NO, NOS has always been one of the research focuses. Specially, nNOS acts as a key role in erection launch, whereas

eNOS enables cavernous body dilate and maintains the status of erection [24]. Although the effect of iNOS was absent in the direct regulation of penile erection, a special "double effect" in the elderly and the pathological state was reported [25]. Since the reduction of NOSs or the decrease of its activity might contribute to ED, the treatment on L-Arg-NO-cGMP for ED might be revolutionary breakthrough, as phosphodiesterase type 5 inhibitors (PDE5Is) was found to improve the erectile function by increasing the NO concentration but reducing the eGMP degradation [26]. However, nearly 20% of patients with ED still showed little benefit after receiving PDE5Iss, especially in patients with diabetes or prostate cancer (Prostate carcinoma) after radical mastectomy [27]. Future NOSs gene transfer therapy from the molecular level would be another choice [28], which might have long-term curative effect, little side effect to the body and, even, completely cure ED. Therapies including increasing expression of NOSs (nNOS, iNOS, eNOS) or inhibiting the expression of protein inhibitor of NOS (PIN) might be promising and worthwhile exploration [29]. However, shortcomings such as short effect duration, possibility of inducing abnormal erection and other potential unknown side effects from the long-term excessive expression of NO are addressed.

2.2. NOS and libido

ED may cause low sexual desire or loss of libido in men [30]. Previous study reported that treatment for ED could somehow retrieve sexual desire [31]. It is believed that NO and NOS are beneficial for penile erection, and consequently, NO and NOS may enhance sexual motivation in indirect ways. NO could also affect libido in the direct ways.

Areas for male sexual behavior in brain distribute NO responsive guanylyl cyclase, which involves cellular events of NO [32], and previous studies showed that the NOS inhibitor N^G-nitro-L-arginine methyl ester (NAME) administered to medial preoptic area by reverse dialysis caused reduced mounting of male rat [32, 33]. Chu et al. further reported that Impaza, a stimulator of eNOS, could raise the sexual incentive motivation rates of male rats through the NO-guanylyl cyclase pathway [34], and nNOS was also considered to affect the male sexual behavior by activating the cyclic guanosine monophosphate (cGMP) [35]. However, adverse result was reported by other researchers, and the conclusion was still controversial [36].

3. NOS and male infertility

Approximately 15% of couples suffer from infertility while male cause contributed to nearly 50% in these infertile couples [37]. Male reproduction is known to involve complicated aspects such as spermatogenesis, sperm dynamics, sperm morphology and acrosome reaction. Increasing evidences have been indicating that NOS and NO are associated with male infertility [38].

3.1. NOS and male reproductive system

The hypothalamic-pituitary axis plays core roles in reproduction and steroid hormone production in man. Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), which is produced and secreted by the arcuate nucleus

of the hypothalamus, could stimulate the anterior pituitary to episodically release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH stimulates the Leydig cells to produce testosterone, and FSH exerts its effect directly on the Sertoli cells to promote spermatogenesis (**Figure 2**).

In vitro studies have shown that NO stimulates LHRH secretion from the hypothalamus and modulates LH release from the pituitary [39, 40]. Ceccatelli [41] reported that sodium nitroprusside, a NO donor, suppressed GnRH-stimulated LH release from pituitaries in male rats. Chatterjee et al. [42] showed that NOS inhibitor p-nitro-L-arginine methyl ester (L-NAME) enhanced GnRH-induced LH release from pituitaries in rats. Decreased level of GnRH and gonadotropin in chronic NO deficiency rats were also observed [43].

3.1.1. Testis

3.1.1.1. Testicular microcirculation

The testis has a rich vascular system that plays a very important role in maintaining the normal functions and stable inner environment of the testis [44]. The regulation of testicular blood microcirculation is very complex, including self-regulation, neural regulation and humoral regulation [45]. NO is the major physiological regulator of basal blood vessel tone and is continually released from endothelium of testicular arteries [46]. A study showed that the regulation effect of NO on testicular blood flow was limited under basal conditions, but this limitation could be significant reversed after HCG treatment; in this case, NO showed

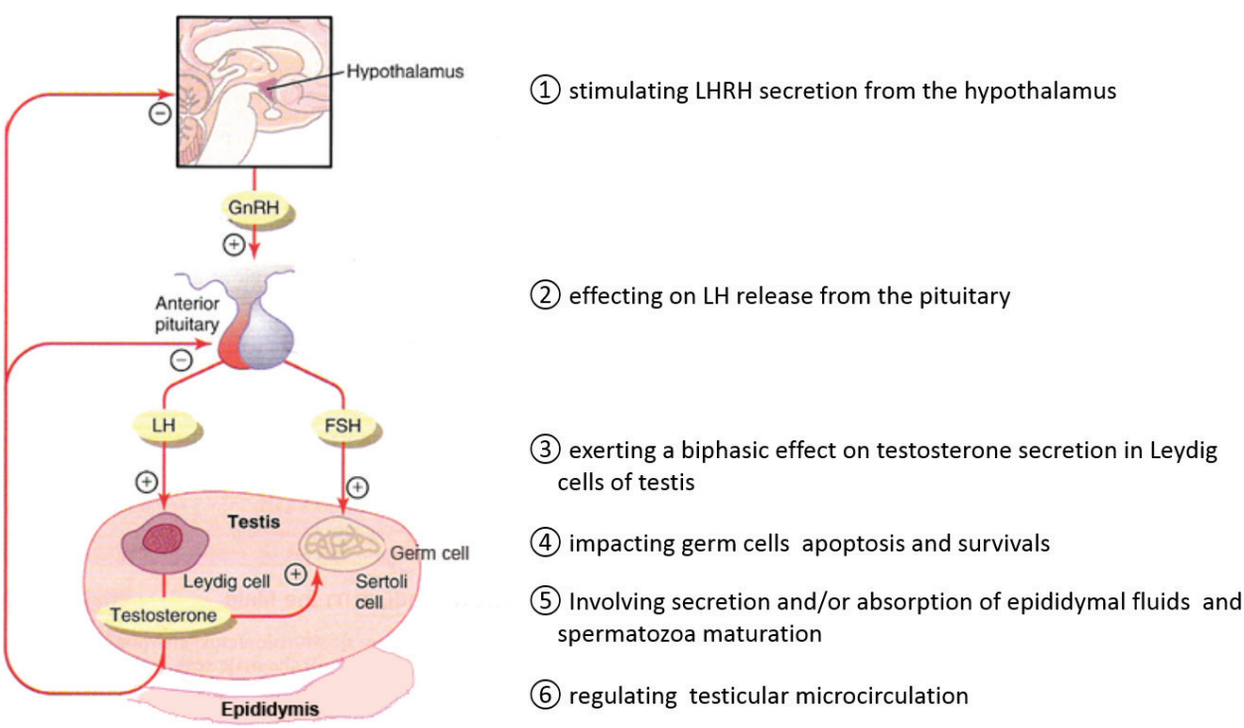

Figure 2. Regulation of hypothalamic-pituitary axis. Abbreviations: LHRH, luteinizing hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

the effects of increasing blood flow and inhibiting leukocyte accumulation on rat testicular arteries [46]. NO is also an important factor in regulating testicular vessel tension at different temperatures, at 34–37°C, disturbance of testicular arteries reaction appeared after L-NAME treatment [47]. Interestingly, NO content and NOS activity could be significantly increased at abnormal high temperatures caused by varicose spermatic veins in varicocele patients [48].

3.1.1.2. Leydig cells

Leydig cells, also known as interstitial cells, are adjacent to the seminiferous tubules in the testicle. Leydig cells produce and release testosterone under the control of LH and act as autocrine and/or paracrine hormones in gonad under the modulation of NO [49]. An immunohistochemistry study demonstrated that eNOS, nNOS and iNOS all expressed in cytoplasm of Leydig cells in rat testis [50]. Interestingly, a testis-specific subclass of nNOS, known as the truncated form of nNOS (TnNOS), has been recently identified as a major contributor to the formation of NO [51]. TnNOS has been found to be localized solely in the Leydig cells of the testes but neither in the Sertoli nor germ cells [51], which enable us to predict that NO may associate with functions of Leydig cells. Kozieł et al. found that NOS was able to act directly within the male gonad by means of regulating androgen secretion though Leydig cells [52]. Another study showed that stress-induced stimulation of the testicular NO signaling pathway leaded to the inhibition of steroidogenic enzymes [53]. But NOS seemingly exerted a biphasic effect on testosterone secretion [54]. At low concentrations, NO exerted a transient stimulatory effect on testosterone secretions mediated by cyclic GMP, whereas at high concentrations, it inhibited steroidogenesis by Leydig cells.

3.1.1.3. Sertoli cells

Spermatogenesis is a complex process in which Sertoli cells closely involve, and NOS also plays a crucial role in this process through Sertoli cells. Zini et al. [55] showed that eNOS protein located in Sertoli cells and some parts of germ cells in seminiferous tubules, especially in degenerating germ cells and spermatids in histologically normal testes. The iNOS was also found in Sertoli cells, as well as a small subset of pachytene spermatocytes and elongated spermatids in the normal testis [56]. However, iNOS expression could be very intense in Sertoli cells in pathological conditions, for example, the absence of seminiferous tubules [57]. iNOS involves in germ cell death in testicular ischemia-reperfusion injury model, and inhibition of iNOS could improve impaired spermatogenesis [58]. In cryptorchidism model, the transgene expression of eNOS increased testicular germ cell apoptosis. In iNOS⁄mice, the numbers of spermatocytes, spermatids and Sertoli cells per tubule were significantly more than those with wild-type testes [59]. A possible conclusion could be drawn that NO plays an important role in both numerical and functional regulation of key somatic cells in the testis, which in turn impacts on germ cells and their survivals during the process of daily sperm production.

3.1.1.4. Epididymis

The main functions of the epididymis are promoting spermatozoa mature and storing spermatozoa [60]. An immunostaining study in human epididymis showed that NOS almost exclusively located in the epithelium [55], and the greatest concentration was in the adluminal

region [55]. It suggests that NOS may involve secretion and/or absorption of epididymal fluids, or in another way diffuse into the tubule lumen to affect nearby spermatozoa. Another study showed a similar distribution of NOS protein in rat epididymis, speculating that epididymal NOS protein might contribute to spermatozoa maturation [61].

3.2. NOS and sperm function

Approximately 15% of couples suffer from infertility while male cause contributed to nearly 50% in these infertile couples [37]. Male reproduction is known to involve complicated aspects, such as spermatogenesis, sperm dynamics, sperm morphology and acrosome reaction. Increasing evidences have been indicating that NOS and NO are associated with male infertility [38].

3.2.1. Sperm motility, morphology and viability

Sperm motility is an essential factor for male fertility. Low sperm motility, also referred as asthenozoospermia, is one of the major causes to male infertility [62]. Previous study indicated that nearly 80% of semen samples from infertile males were defective in sperm motility [63]. Hellstrom et al. reported for the first time that sodium nitroprusside, a NO releaser, was beneficial for maintenance of thaw-sperm motility by reducing lipid peroxidative damage to sperm membranes. Significantly improved motion parameters of sperm were observed in semen samples treated with sodium nitroprusside in concentrations of 50 and 100 nM compared to control samples, and this beneficial effect maintained for 5–6 hours after thaw [64]. However, NO concentration in normozoospermic fertile men was observed to be significantly lower than those of asthenospermia infertile men [65]. In fact, the effect of NO seems to be double-sided, low concentration of NO improves sperm motility, while high concentration contributes to adverse effect [66]. Herrero et al. reported that a significant decrease on sperm motility was observed in semen samples treated with sodium nitroprusside in a higher concentration of 300 mM, and this effect could be blocked by hemoglobin, a scavenger of NO, as sperm motility in samples furtherly treated with hemoglobin was significantly higher than those without. While when the incubating concentration of sodium nitroprusside reduced to 150 mM, no modifications of sperm motility were found [67]. Besides, the other NO releaser, S-nitroso-N-acetylpenicillamine (0.012–0.6 mM), along with sodium nitroprusside (0.25–2.5 mM), was found to decrease percentage of forward progressive sperm motility and straight line velocity in a concentration-dependent manner [68].

As to sperm morphology and viability, the effects of NO reveal controversial contributions. a positive correlation between NO with defects in sperm morphology has been found in male with normal sperm rate ≥14% but a negative correlation with defects in sperm morphology in male with normal sperm rate <14% [69]. However, later study failed to find any significant association between NO production and sperm morphology [70]. Researchers reported that semen treated with 0.25–2.5 mM sodium nitroprusside revealed significantly less sperm bound to the zona pellucida compared with the control group which treated without NO [71], whereas some other researchers reported no any significant effect of NO on sperm viability [66, 69, 72]. And meanwhile, low concentration of NO also plays a role in the maintenance of sperm viability after cryopreservation and post-thaw sperm [65, 66, 68].

3.2.2. Capacitation, hyperactivation and acrosome reaction

Capacitation is a process in which spermatozoa acquire the ability to bind to the egg's zone pellucida and fertilize an oocyte during their transit in the female genital tract [73, 74]. Capacitation involves in some molecular events, and it was clear that low level of NO from NO-releasing agents induces human sperm capacitation [75]. Indeed, it has been reported that NO-releasing compounds significantly benefit the capacitation, whereas NO inhibitors decrease this process [76]. In fact, NO produced by spermatozoa involves in a cascade of molecular events of capacitation, which is needed over the course of this process [77–79].

Hyperactivation can be treated as a subcategory of capacitation. Hyperactivation of spermatozoa exhibits high amplitude and asymmetric flagellar movement, non-linear motility and penetrate the oocyte with strong propulsive force [70, 80]. The effect of NO on hyperactivation was found to be similar to which on sperm motility, little concentrations of NO increased spermatozoa hyperactivation, whereas excessive concentrations decreased the hyperactivated spermatozoa motility [81, 82].

Acrosome reaction denotes the process that capacitated and hyperactivated motility sperm binds to the zona pellucida and continues to pass through the exocytotic release of proteolytic enzymes from the acrosome so that to bind to the mature ovum. The amount of NO influenced the acrosome reaction, and increased amount of sperm was observed to undergo the acrosome reaction with the presence of NO donor compound [83]. Meanwhile, significantly increased amount of sperm was found to bind to membrane of the ovum with their plasma membrane [84].

3.2.3. Sperm mitochondria

Mitochondria in sperm activate as a generator which supply sperm with energy for the process of motility, acrosome reaction, oocyte fusion, fertilization and so on [85]. NO has been reported to involve in functions of mitochondrial that include biogenesis, remodeling and mitochondrial respiration [86–88]. Specially, different levels of NO could cause different sperm mitochondrial functions, low concentrations of NO enhanced the sperm motility, while NO with higher levels cause mitochondrial hyperpolarization and sperm apoptosis [64, 89]. This might explain the adverse effects of various concentrations NO on sperm motility.

3.3. Single-nucleotide polymorphisms of NOS and male infertility

Genetic variations are crucial etiological factors contribute to male infertility. Up to date, some single-nucleotide polymorphisms (SNPs) have been identified to involve in sperm defects and male infertility in ethnic populations. Polymorphisms T786C and G894T of eNOS were reported to decrease sperm motility and quantity by increasing the seminal oxidative stress in Egyptian infertile male population [90]. Similar results of G894T were reported in Italian and Iranian infertile male populations [91, 92], and this SNP also found to be associated with higher level of sperm DNA fragmentation in Chinese infertile males [93]. The polymorphism 4a4b, which refers to a sequence variant with variable sequence of tandem 4a4b repeats in intron 4, was found to be associated with poor sperm morphology and male infertility in a

Korean and Chinese population [94, 95]. Associations between SNPs of NOS and male infertility are under exploration, which would be promising tools for diagnosis or further curing male infertility.

3.4. Possible therapy strategies of NOS on male infertility

Increasing evidences has been showing that inappropriate concentration level of NO may contribute to male infertility in some extend by means of decreasing sperm motility and normal sperm morphology, reducing efficiency of capacitation and acrosome action. It is reasonable to consider possible therapy strategies to the utilization of NOS donors or inhibitors so that to adjust the concentration of NO to the "right" level. In fact, significantly higher fertile rate was observed in animal experiment in vitro, and further researches would be needed to warrant the potential benefits for human beings.

4. NOS and prostate carcinoma

Prostate carcinoma is one of the most common cancers among men and second in cancer-related deaths in the United States. An estimated study predicted that there will be 180, 890 new prostate carcinoma cases and 26, 120 deaths due to the disease in the country in 2016 [96]. Etiological studies implicated that multiple reasons involved in prostate carcinoma susceptibility, such as dietary, environment, hormone status and genetic factors [97]. Growing studies indicated that NOS and NO system play crucial roles in progression of human prostate carcinoma [98–100].

The physiological functions of NO are dependent primarily on concentrations. Low concentration of NO acted as a signal transducer and affects many physiological processes including blood flow regulation, platelet activity, iron homeostasis, cell proliferation and neurotransmission, whereas, in high concentrations, it exerted a cytotoxic protective effect, for example, to against pathogens and perhaps tumors [101, 102].

4.1. Role of nitric oxide synthase in cancer biology

The roles of NOS and NO on DNA damage, apoptosis, cell cycle, enhancement of cell proliferation, angiogenesis and metastasis are currently viewed, and NO was found to be associated with tumor environment, for example, the vasculature cells and other stromal cells [103–105]. Research also indicated that NOS2 expression was correlated with tumor vascularization, accumulations of p53 mutations and activation of epidermal growth factor receptor, even could be treated as an independent predictor of poor survival in women with estrogen receptor (ER)-negative breast tumors [106]. Low concentrations of NO acted as a promotional role in angiogenesis which stimulates tumor progression by providing blood flow access to the tumor and subsequently resulting in cell proliferation. On the contrary, high levels of NO tend to be cytotoxic to cancer cells [107]. While in animal models, iNOS overexpression produced either pro-tumor or anti-tumor effect on tumor growth, these alterable effects seem to be dependent on the tumor microenvironment and the tumor type itself [104, 108]. The effects

of NO possibly differ in expression level of iNOS, duration and timing of NO delivery, the microenvironment, the genetic background and the cell type (**Figure 3**) [109].

4.2. NOS and proliferation of prostate carcinoma

NO generated by eNOS or iNOS might be involved in prostate proliferation. At low concentrations, NO acted as a signaling molecule regulating smooth muscle relaxation and blood flow, neurotransmission, platelet activity, iron homeostasis, cell survival and proliferation, while at high concentrations acted as modulating immune-mediated anti-tumor activities [110, 111]. Concentration of NO less than 100nM had an effect of preventing certain cell types from apoptosis and thereby favors tumorigenesis and progression [112]. Higher expression of iNOS was detected in cancer specimens than that in normal tissues of prostate carcinoma patient. Aaltoma et al. also demonstrated a positive association between expression level of iNOS and rapid cancer cell proliferation rate, dedifferentiation and advanced stage cancer [113]. A recent study has shown that NO also regulated cell proliferation in a pathway of CPD-Arg-NO [114].

4.3. Nitric oxide synthase and angiogenesis of prostate carcinoma

Angiogenesis is a critical molecular event in tumor progression [115, 116]. Epidermal growth factor receptor (EGFR) signaling pathway, tumor suppressor p53 and VEGF, which are collective mediators that exacerbate angiogenesis can be stimulated by NO [115, 117]. The involvement of eNOS in the NO-induced human endothelial and prostate carcinoma cell migration was further warranted [116]. Recent research also reported that NO played vital roles in maintaining blood supply for prostate carcinoma, and an anti-tumor vascular activity effect revealed with presence in inhibition of NOS [115].

4.4. Single-nucleotide polymorphisms of NOS and susceptibility of prostate carcinoma

Several studies suggested that polymorphisms of some NOS genes were genetic susceptibility factors for prostate carcinoma, especially for aggressive diseases [118, 119]. A plethora of meta-analyses has identified eNOS gene polymorphisms as strong susceptibility factors for the progression toward prostate carcinoma [120]. Another study also reported that NOS3 gene

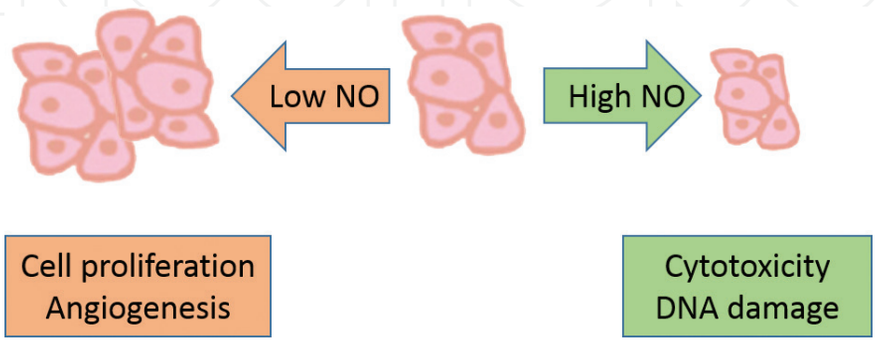

Figure 3. Roles of NO in prostate cancer. Abbreviation: NO, nitric oxide.

polymorphisms were genetic susceptibility factors for the progression of prostate carcinoma and poor patient outcomes [121]. A meta-analysis conducted by Zhao et al. suggested that eNOS gene 894G > T polymorphism contributed to aggravate the onset of prostate carcinoma in males [122]. Nikolic et al [123] also corroborated the involvement of eNOS or NOS3 gene in the pathogenesis of prostate carcinoma. NOS3 rs1799983 polymorphism augmented the risk of prostate carcinoma in various populations. As one of the possible mechanisms, the involvement of NO receptor component, sGC-1, in mediating the proliferation of prostate carcinogenesis, has been surmised [124].

4.5. Possible therapy strategies of NOS on prostate carcinoma

Anti-cancer agents such as gold lotion have successfully demonstrated their anti-carcinogenic potential through the regulation of both iNOS and eNOS [125–127]. Yu et al. [128] also elucidated the significance of eNOS as a seemingly promising strategy for targeting anti-androgen resistant prostate carcinoma. Arginine-releasing compounds such as carboxypeptidase-D increased NO production, which slackened progression of prostate carcinoma so that prolonged survival time [129]. NO-donor drugs also have been under increasing explorations. A few NO-donor drugs have been confirmed to have favorable anticancer activity and could be potential anticancer therapies [3, 130]. GIT-27NO, a novel NO donor, inhibited the growth of PC3 and LnCap prostate carcinoma cells xenografted into nude mice in a concentration-dependent manner [131]. And DETA-NONOate was revealed to inhibit epithelial-mesenchymal transition (EMT) and invasion of human prostate metastatic cells by producing large amount of NO [132]. It is sensible that novel NOS-based therapeutics may prove valuable in the future treatment of prostate carcinoma.

5. NOS and other urinary and male reproductive diseases

5.1. Peyronie disease

Peyronie disease (PD) is an intractable, sexually dysfunctional disease resulting in penile curvature, penile pain, penile deformity, difficulty with coitus, shortening, hinging, narrowing and ED. Mechanisms of PD have not been fully elucidated. A recent hypothesis was that the recurrent microtrauma of the tunica albuginea caused small damages that activated processes of wound healing and fibrotic plaque development during sexual intercourse [133]. Inflammatory cells and iNOS accumulated in the process of wound healing, the increased NO then led to the myofibroblasts and proliferation of fibroblasts and redundant collagen between the layers of the tunica albuginea (penile plaque) [134]. Although surgical therapy is now the first-option for PD patients, researchers are focusing on the nonsurgical treatments of PD, and NOs inhibitors might be a promising choice [135].

5.2. Priapism

Priapism is defined as a persistent and painful erection that lasts longer than 4 hours without sexual stimulation and can lead to ED [136]. The relation between penile erection and production of NOS has been well investigated: nNOS and eNOS were the causes of both the initiation

and maintenance phases of penile erection [137]. However, decreased function in NO generated by decreased activation of eNOS resulted in PDE5 downregulation that was thought to be a derivate of NO and, therefore, reduced basal levels of PDE5 and caused priapism [138].

5.3. Cryptorchidism

Cryptorchidism denotes failure of the movement of the testis to the scrotum, and in most cases, it raises risk of testicular germ cell cancer and subfertility later in patients' life course. Testicular germ cell apoptosis which causes by exposure of testicular in elevated temperature and oxidative stress is the primary etiology of infertility. Animal models with cryptorchidism induced by surgery revealed that eNOS played a significant role in mouse spermatogenesis in cryptorchidism-induced apoptosis [139]. Contemporaneously, reduced rate of testicular atrophy was observed in heterozygous Hoxa 11 knockout mice which had congenital bilateral cryptorchidism when early treated with Nomega-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor [140].

6. Conclusion

It has been becoming evident that redox regulation driven by NOS and NO represents a promising tool for exploring fundamental diseases process and new development of strategies to treat urinary, male reproductive and sexual diseases.

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