NGF and the Male Reproductive System

Subjects: Neurosciences | Andrology

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Infertility is a worldwide health issue defined by the World Health Organization (WHO) as the inability to establish a pregnancy after 12 months or more of regular and unprotected sexual intercourse. Male infertility etiology can be related to either congenital or acquired factors. The therapeutical approach to male infertility depends on the underlying causes and includes medical and surgical treatments. The potential role of nerve growth factor (NGF) in male reproductive physiology has been proposed. It has been hypothesized that neurotrophins might be involved in testis morphogenesis and regulation of several aspects of spermatogenesis. Moreover, it has been shown that NGF exerts its role on gonadotropin-releasing hormone (GnRH) neurons through the activation of the PKC/p–ERK1/2/p–CREB cascade, which leads to the activation of hypothalamic cells and the consequent activation of hypothalamus–pituitary–gonadal axis (HPG) with the secretion of GnRH.

Keywords: male infertility ; oligozoospermia ; asthenozoospermia ; azoospermia ; sperm cryopreservation ; assisted reproduction ; nerve growth factor ; neurotrophins

1. Introduction

During the past years, there has been growing interest in the understanding of male infertility causes and treatments. Infertility has an important social impact because it can affect mental health, being related to depression, anxiety disorders, and other psychological diseases. According to the WHO, the quality of life and psychological health depend directly on sexual health. Many factors can be related to male infertility, such as hormonal disease, obesity, diabetes, ejaculatory disorders, urogenital infections, testicular trauma, chemo/radiotherapy, or surgical treatments.

Recent findings reported the implication of nerve growth factor (NGF) in male reproductive pathophysiology. A wide number of animal and human studies demonstrated the involvement of NGF in spermatogenesis, testis morphogenesis, and the hypothalamus–pituitary–gonadal (HPG) axis and its improving effect on sperm traits. Therefore, NGF might be exploited in male infertility treatment, suggesting potential new strategies for male infertility therapy.

1.1. Male Infertility

1.1.1. Epidemiology

Infertility is a worldwide health issue defined by the World Health Organization (WHO) as the inability to establish a pregnancy after 12 months or more of regular and unprotected sexual intercourse [1][2]. Infertility affects approximately 15% of reproductive-aged couples and 186 million individuals globally [3]. Data suggest that in about 50% of infertility cases, “male factor” infertility has an important role and is solely responsible in 20–30% of cases [4]. Infertility is related to psychological distress, leading to depression and anxiety disorders, and has an important social impact [5][6].

1.1.2. Etiology

The etiology of male infertility can be related to a variety of factors, which can be distinguished into congenital or acquired [2]. Both congenital and acquired causes of male infertility can be classified into three categories: pretesticular, post-testicular, and testicular causes [7]. Among the pretesticular causes of male infertility, hypogonadotropic hypogonadism (HH) is one of the main causes [8]. Patients affected by HH have a deficit of LH and FSH secretion, which can be due either to a pituitary or hypothalamic dysfunction [9][10].

The hyposecretion of LH and FSH compromises normal spermatogenesis and production of testosterone, being responsible for infertility [11][12]. Other pretesticular causes of male infertility are coital disorders, such as ejaculatory disorders (e.g., anejaculation, retrograde ejaculation) [13][14] and erectile dysfunction [15]. It should be noted that some authors included coital disorders among the post-testicular causes of male infertility [16]. Post-testicular causes of male

infertility also include primarily all the obstructions of the seminal tract [17][18]. Infections of the urogenital tract are also among the post-testicular causes of male infertility; in fact, microorganisms and leucocytes in the semen might damage sperm motility [19][20]. Moreover, activated leucocytes might produce reactive oxygen radicals (ROS), inducing sperm cell dysfunction [21].

Furthermore, inflammatory diseases of the accessory glands (e.g., prostatitis) and autoimmune reaction against the spermatozoa are included in the post-testicular causes of male infertility [22]. Post-testicular diseases might also be congenital, as in the case of CAVD (congenital absence of the vas deferens) [23]. Lastly, male infertility can be due to primitive testicular dysfunction, which causes impaired sperm production [24].

Testicular causes of male infertility include orchitis, testicular trauma, torsion, cryptorchidism (congenital or acquired) [25][26][27], systemic diseases, iatrogenic forms, and genetic abnormalities. Varicocele can be considered a cofactor of defective sperm production because it is associated with testicular atrophy and Leydig cell dysfunction [28]. In about 50% of cases, the etiology of male infertility still remains unknown (idiopathic infertility) [29]. Idiopathic infertility is probably, in most cases, related to genetic causes, considering that more than one thousand genes are involved in spermatogenesis [30].

1.1.3. Treatments

The therapeutical approach to male infertility depends on the underlying causes and includes medical and surgical treatments [31]. Medical treatment of male infertility mainly involves hormonal treatment [32], which is based on the use of gonadotropin-releasing hormone (GnRH), gonadotropins, testosterone, dopamine agonists, aromatase inhibitors (AI), and selective estrogen receptor modulators (SERMs) [33].

Men affected by hypogonadotropic hypogonadism related to a reduced secretion of GnRH from the hypothalamus can be treated with GnRH therapy [34]. The pulsatile administration of GnRH stimulates the anterior pituitary to release gonadotropins [35], with the re-establishment of the hypothalamus–pituitary–gonadal (HPG) axis leading to high levels of testosterone and stimulation of Sertoli cells by the FSH [36]. In about 85% of patients treated with pulsatile GnRH, spermatogenesis is induced [37][38][39].

The administration of gonadotropins can be useful in men with hypogonadotropic hypogonadism related to pituitary dysfunction. It has been shown that gonadotropin therapy induces spermatogenesis in about 80% of patients [40][41]. Dopamine agonists are used for the treatment of male infertility associated with prolactin-secreting pituitary adenoma [42]. SERMs are indicated for the treatment of idiopathic infertility [43]. Their action is based on the inhibition of central estrogen feedback upregulating the production of pituitary gonadotropins [44]. Surgical therapy for male infertility is indicated mainly in men with obstructive azoospermia (OA) [45][46].

When treatment has failed or no specific treatment is available for the condition underlying male infertility, assisted reproductive technologies (ARTs) are indicated [47]. Among them, the most used and successful are intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) [48][49].

IUI is a technique that involves the introduction of spermatozoa through the cervix using a catheter [50]. This technique is indicated in case of mild male infertility or unexplained infertility [51]. However, IUI needs a good semen quality and thus it is not fully indicated for “idiopathic oligozoospermia and asthenozoospermia or in men affected by retrograde ejaculation and anejaculation [51][52].

IVF facilitates fertilization by bringing the spermatozoa close to the oocyte [52] occurring outside the female body. IVF techniques usually include (i) a transvaginal ovum retrieval whereby a small needle is inserted through the back of the vagina and guided via ultrasound into the ovarian follicles to collect the fluid that contains the eggs and (ii) an embryo transfer whereby one or several embryos are placed into the uterus of the female with the intent to establish a pregnancy.

ICSI is the treatment of choice in case of IVF failure [53] and it consists of the injection of a single spermatozoon directly into the oocyte’s cytoplasm [54]. It can be used with ejaculated sperm, epididymal sperm, or testicular sperm. Retrieved epididymal or testicular spermatozoa are often cryopreserved to avoid repeated aspirations or biopsy in case of ART failure [55].

2. NGF

2.1. Neurotrophins

Neurotrophins are a family of growth factors mainly involved in the regulation of neuronal survival, function, and plasticity within the central and peripheral nervous systems. Neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) [56]. These factors exert their effects by binding two major receptor types: the p75 neurotrophin receptor (p75NTR) and the tropomyosin-related tyrosine kinase (Trk) receptors. P75NTR is a low-affinity receptor to which all neurotrophins can bind; neurotrophins, in the absence of Trk receptors, can bind to p75NTR, which acts as a death receptor.

Trk receptors are a family of three receptors including TrkA, which functions mainly as a receptor for NGF, TrkB (as a receptor for BDNF and NT-4), and TrkC (as a receptor for NT-3) [57]. Neurotrophins binding to Trk receptors activate different intracellular signaling cascades, including Ras/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B-mammalian target of rapamycin (PI3K/Akt-mTOR), and phosphoinositide-specific phospholipase C-γ (PLC-γ) pathways [58][59][60]. The activation of the Ras/MAPK and PI3K/Akt pathways is involved in promoting neuronal differentiation and survival [61][62]. PLC-γ pathways trigger the intracellular release of calcium ions from the endoplasmic reticulum, leading to the activation of calcium-dependent proteins and the expression of transcription factors and ion channels [63][64][65].

Among the neurotrophin family, nerve growth factor (NGF) was the first to be discovered. It was identified in the early 1950s by Rita Levi-Montalcini in mouse sarcoma cultures [66]. NGF shows neuroprotective and neurotrophic effects in the central nervous system and regulates the survival and maturation of developing neurons within the peripheral nervous system [67][68]. Moreover, NGF is involved in the neural response to damage in nociceptive sensory neurons, Schwann cells, and α motor neurons [69][70][71][72]. Neurotrophins are mainly known for their neurotrophic role, but they also exert a variety of effects outside the nervous system [73][74]. Changes in NGF in the serum and plasma were shown during the beginning and progression of many pathologies, including neurological, psychiatric and immune diseases [75][76], and physiopathological conditions, such as cardiometabolic disruptions [77][78], oxidant circumstances [79][80], stressful events [81][82], alcohol addiction [83][84][85], and aging [86][87][88].

Indeed, the expression of neurotrophin receptors in several non-neuronal tissues and the involvement of neurotrophins in essential non-neuronal functions, such as the maintenance of immune cells, has been demonstrated. In particular, NGF induces the differentiation of B lymphocytes [89] and is involved in the maintenance of neutrophils, peritoneal mast cells, and B lymphocytes [90][91][92].

2.2. NGF Expression in the Reproductive System

It is known that NGF plays a pivotal role in regulating neuronal cell growth and survival; increasing evidence shows that NGF also exerts a variety of effects on non-neuronal cells. In recent studies, the expression of NGF and its receptors (TrkA and p75NTR) outside the nervous system has been demonstrated, in particular in the male reproductive system [93][94][95][96], leading to the hypothesis that NGF could have a role in the reproductive system [97][98]. Moreover, pieces of evidence show that the testis and brain share a common embryonic origin [99][100], explaining the expression of neural receptors in sperm cells [101].

Ayer-LeLievre et al., in 1988, demonstrated that in testis and epididymis of rats and mice, NGF and TrkA were expressed [102]. Successively, a large body of studies confirmed these results. The presence of NGF was first detected in the prostate of guinea pigs [103], rabbits, and bulls [104]. In a study conducted on golden hamsters, it was found that NGF expression is greater in the caudal portion of the epididymis than in the other regions [105]. Many studies conducted on a variety of species, such as camelids, llamas, rabbits, and alpacas, demonstrated the presence of NGF and its receptors in seminal plasma [106][107][108][109][110]. In 2010, Li et al. reported the presence of NGF, TrkA, and p75NTR in the spermatozoa's tail and head. Moreover, they showed that oligo/asthenozoospermic men had lower levels of NGF in their semen compared to fertile men [111]. All these findings suggest the potential role of NGF in male reproductive physiology [112][113].

3. NGF Specific Functions in the Male Reproductive System

3.1. NGF's Role in Testis Morphogenesis

It has been demonstrated that neurotrophins are involved in the morphogenetic process regulating local cell–cell interactions in many tissues, such as kidney, tooth, dermatome, and ovary [114][115][116][117]. Moreover, neurotrophins play

a role in germ cell survival and differentiation [118]. Therefore, it has been hypothesized that neurotrophins might be implicated in testis morphogenesis. The expression of neurotrophins in postnatal testis has been shown [102][119][120].

The expression of p75NTR in the mesenchymal tissue that surrounds the testis cord has been observed [121][122]. Levine et al. studied the effects of neurotrophins on seminiferous cord formation using the Trk-specific inhibitor K252a and the inhibitory TrkC-IgG antagonist [123]. They demonstrated that the inhibition of the neurotrophin pathway resulted in an inhibition of testis cord formation, suggesting that neurotrophins play a crucial role in testis morphogenesis [124].

Cupp et al. studied the role of TrkA and TrkC in the process of testis development, finding that TrkA is involved in the early stages of testis morphogenesis, whereas TrkC is involved in the later stages, both being implicated in the regulation of the germ cells number [125].

3.2. NGF Role in Spermatogenesis

Spermatogenesis involves a complex system of processes that lead to the production of mature spermatozoa in the seminiferous tubules (ST) [126][127]. The spermatogenic process requires three crucial steps: the mitotic division of spermatogonia [128]; meiosis I, with the generation of spermatocytes, and meiosis II, with the generation of spermatids [129]; and spermiogenesis, culminating in the production of mature spermatozoa [130]. Spermatogenesis is regulated by both endocrine and paracrine mechanisms [131][132].

The hormonal control is mediated by follicle-stimulating hormone (FSH) and testosterone [133]. The paracrine mechanism of regulation of spermatogenesis is mediated by Sertoli cells and germ cells [134], which are involved in the production of a variety of regulatory factors [135][136]. The proteins secreted by germ cells exert their effect on Sertoli cells, stimulating them to produce many molecules involved in the process of spermatogenesis, such as ABP [137], transferrin [138][139], IL-1a [140], SGP-2/1 [141], inhibin [142], and ceruloplasmin [143]. Moreover, germ cells inhibit the production of 17b-estradiol [144].

The process of spermatogenesis requires a synergic and/or redundant action of regulatory molecules in order to occur correctly [145][146]. Among these molecules involved in spermatogenesis regulation, there is growing attention on neurotrophins. The presence of different neurotrophins in mammalian testis has been demonstrated [147], but among them, the NGF is the only one that showed a potential role in spermatogenesis.

Many studies indicated the impact of NGF on several aspects of spermatogenesis. The presence of NGF protein [148] and mRNA [102] in germ cells has been shown, and its mitogen activity has been demonstrated [118]. NGF shows different effects, such as guaranteeing the physiological integrity of seminiferous epithelial cells [149], stimulating DNA synthesis within the seminiferous tubules [150], and inducing the secretion of ABP from Sertoli cells [120]. These effects are exerted through the binding between NGF and its receptors, p75NT and Trk [119][151], which are expressed on Sertoli cells.

The presence of NGF receptors on Sertoli cells in animals' testis suggested the role of NGF in spermatogenesis regulation. Subsequently, the presence of NGF mRNA and p75NTR mRNA and protein in human testis was demonstrated [152][153].

3.3. The Impact of NGF on the Hypothalamus-Pituitary-Gonadal (HPG) Axis

Spermatogenesis is regulated by the hypothalamus–pituitary–gonadal (HPG) axis [154]. The hypothalamus produces gonadotropin-releasing hormone (GnRH) and releases it in a pulsatile manner [155]. The pulsatile secretion of neuropeptide is essential for stimulating the gonadotropic cells of the anterior pituitary to synthesize and secrete LH and FSH [156].

The stimulus of LH and FSH on testis cells activates two crucial endocrine signals: LH stimulates the production of testosterone from Leydig cells [157], and FSH induces the production of ABP (androgen-binding protein) and inhibin from Sertoli cells [158]. FSH and LH have a pivotal role in regulating spermatogenesis, mainly because they mediate the production of Sertoli factors, respectively, in a direct or indirect (through a testosterone–androgen receptor) way [159]. The HPG axis is finely regulated by a negative feedback mechanism [160].

Testosterone, in high levels, inhibits the hypothalamic secretion of GnRH and the pituitary secretion of LH [161]. Inhibin acts on the anterior pituitary, inhibiting the production of FSH [162]. The NGF is involved in the regulation of the hypothalamus–pituitary axis [163][164]. Luo et al. in 2018 demonstrated that NGF can activate GnRH neurons in the hypothalamus and, thus, regulate the hypothalamic secretion of GnRH [165]. Moreover, they found that by using TrkA inhibitors, the effects of NGF on the HPG axis were extinguished. This finding led to the hypothesis that the impact of NGF on the hypothalamic secretion of GnRH was mediated by the TrkA receptor (see **Figure 1**).

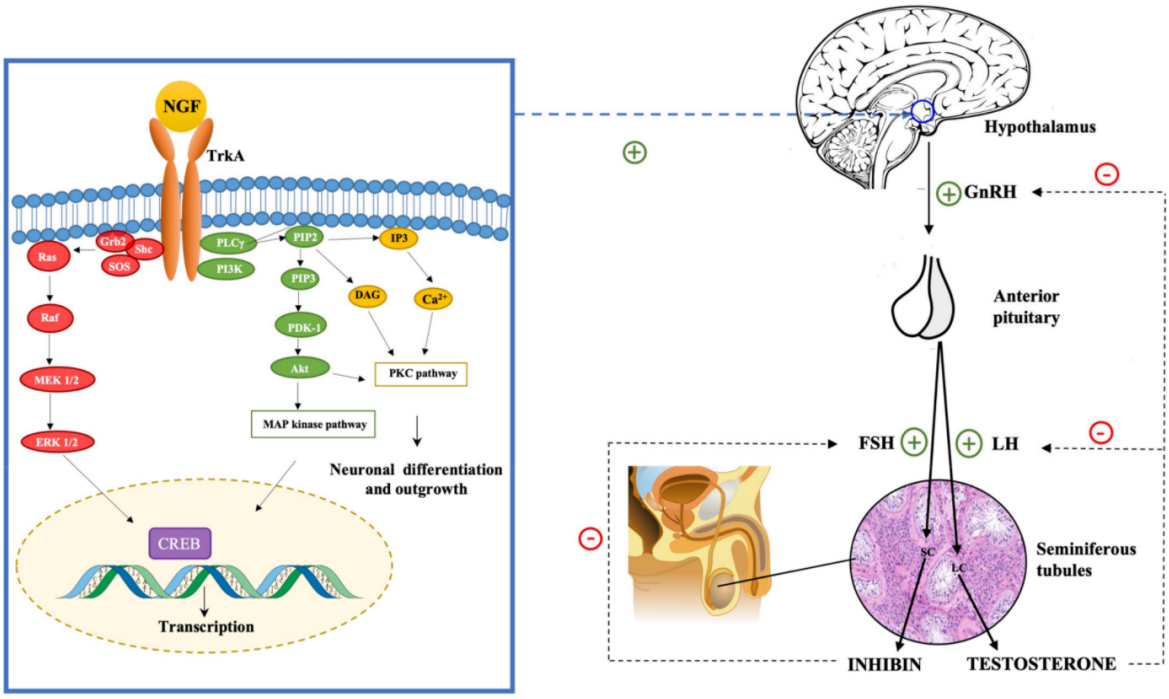

Figure 1. NGF regulates the hypothalamus–pituitary–gonadal (HPG) axis stimulating the hypothalamic production of GnRH. The binding of the NGF to the TrkA receptor activates many intracellular pathways, including the PI3Kinase pathway, which leads to the activation of Akt kinase, the Ras pathway, which leads to MAP kinase activation, and the PLC pathway, which leads to the activation of PKC. These intracellular pathways are involved in regulating the expression of neuronal survival and differentiation genes and the transcription of GnRH gene and neuropeptide production.

The binding of NGF to TrkA activates many intracellular signaling cascades, such as MAPK, PI3K, and PLC-γ-PKC pathways [166]. GnRH transcription and neuropeptide production in GT1-7 cells are regulated by PKC, PKA, and MAPK pathways [167][168]. TrkA activation leads to the activation of ERK1/2 and ERK5. These kinases phosphorylate and activate CREB, Elk-1, and MEF2, which are transcription factors involved in regulating the expression of neuronal survival and differentiation genes [61][169]. The NGF exerts its role on GnRH neurons through the activation of the PKC/p-ERK1/2/p-CREB cascade, which leads to the activation of hypothalamic cells and the consequent activation of the HPG axis with the secretion of GnRH [170][171].

3.4. NGF Effects on Sperm Traits

Various studies demonstrated that nerve growth factor (NGF) exerts a variety of effects on mature sperm traits [172]. the expression of NGF receptors in sperm cells has been demonstrated: p75NTR is mainly in the midpiece and tail, whereas TrKA is expressed in the head and acrosome [173]. In 2010, two different studies reported the presence of NGF and the expression of TrkA receptor in animal sperm. One group studied hamster sperm, demonstrating that the NGF stimulates acrosome reaction and increases sperm motility (see **Figure 2**).

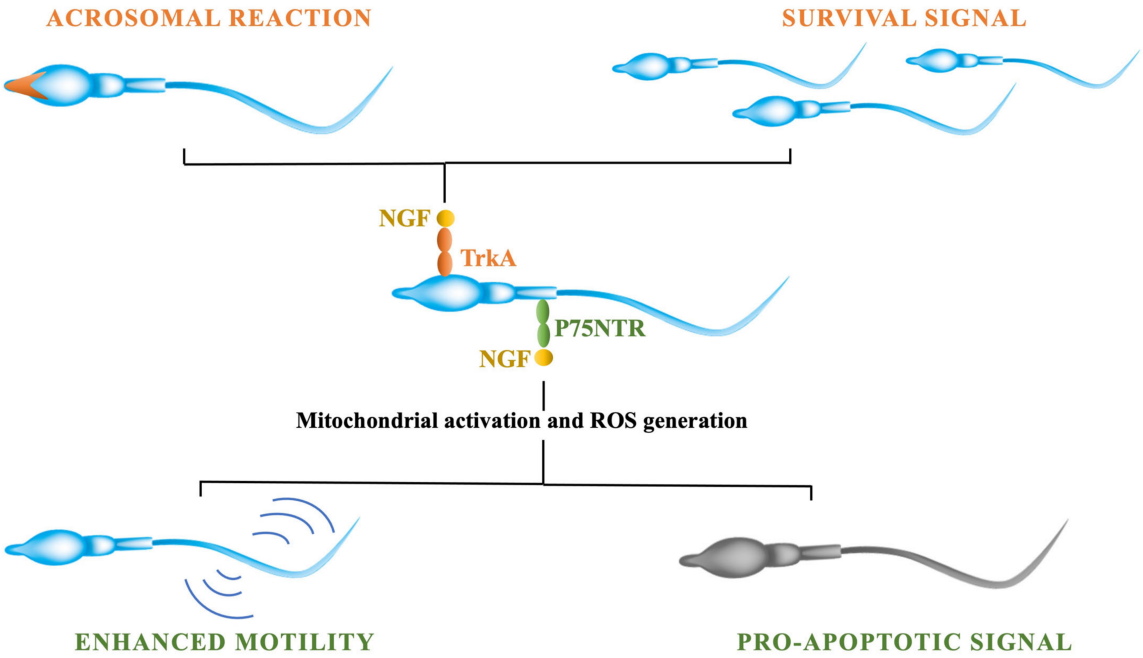

Figure 2. NGF exerts its effects on sperm cells through its binding to its two receptors: TrkA and p75NTR. The activation of the TrkA receptor is involved in stimulating cells' survival and modulating the acrosomal reaction through the activation of the kinases' pathway. The binding of the NGF to p75NTR receptor, instead, is involved in modulating sperm cells' apoptosis by triggering the mitochondrial activity and the production of ROS. Moreover, the activation of p75NTR is involved in modulating sperm motility through the activation of the sperm's respiratory chain.

This stimulating effect of NGF on sperm motility was found to be time- and dose-dependent. The other group studied bovine sperm, demonstrating the presence of NGF and TrkA receptors in ejaculated sperm. They showed that exogenous NGF had positive effects on sperm viability and apoptosis, although the NGF did not affect acrosome reaction [174]. Two years later, a study on human sperm was published; it reported that NGF has an improving effect on human sperm motility traits, such as straight-line velocity, curvilinear velocity, average path velocity, linearity, and beat-cross frequency [175]. After incubating the sperm in vitro with NGF, the sperm motility increased in a dose-dependent manner [176]. Bezerra et al. studied the proteome of seminal plasma in rabbits and suggested that NGF expression might increase sperm motility [177].

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