Chapter

A Review of Sympathetic and Parasympathetic Innervation in the Structural and Functional Maintenance of the Male Gonad

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Abstract

The nervous system controls and coordinates the functions of all body systems, including the male reproductive system. The male gonad, responsible for spermatogenesis and steroidogenesis, receives autonomous sympathetic and parasympathetic innervation, having a great influence on the structural and functional integrity of this organ. The testis receives autonomic innervation primarily at the superior and inferior poles, specifically by the superior and inferior spermatic nerves. This nervous control is wired into all testicular cell populations such as contractile cells (myoid cells), germ cells, and steroidogenic cells. Many studies have also described the influence of autonomic innervation on Sertoli cell control. Thus, any possible interference of physical or chemical agents whose action is directly or indirectly linked to the nervous control of the testicle can result in changes and/or damage to male reproduction, with emphasis on testicular impairment. The present chapter consists of a review of data about the effects of physical or chemical alterations on the autonomous innervation and its repercussions on male gonad. For this, it is necessary to understand the general aspect of the nervous system and the male gonad morphology and innervation, as well as the action of drugs or any methods that promote changes in the communication between these two systems.

Keywords: sympathetic innervation, parasympathetic innervation, testis, reproduction, testosterone levels

1. Introduction

The nervous system exerts the control and coordination functions of all body systems, including the male genital system. It can be divided into two main parts: central nervous system (CNS) and peripheral nervous system (PNS), according to anatomical characteristics [1]. The PNS, in turn, is divided into afferent and efferent

parts, where the autonomic nervous system is found [2]. This autonomic nervous system is responsible for the involuntary control of several body activities, including smooth muscle contraction and secretory activity of glands [3].

The internal male genital system of most mammals is composed of a pair of testes (gonads), epididymis and deferent ducts, in addition to accessory sex glands (prostate and seminal gland). It is known that this system is directly controlled by the neuroendocrine system, mainly the testis [4]. The testicle is an organ of the male genital system that can be structurally and functionally divided into two parts: seminiferous tubules and interstitium, responsible for the production of sperm and steroid hormones, respectively [5, 6].

In fact, the male genital tract receives autonomous sympathetic and parasympathetic innervation, having a great influence on the structural and functional integrity of the organs that compose it [7–12]. In general, parasympathetic fibers reach the target organs of the male genital system via the pelvic plexus via the pelvic nerves. In contrast, sympathetic fibers reach their target organs via thoracolumbar segments, via the hypogastric nerves that originate from the inferior (caudal) mesenteric ganglion [13, 14].

Therefore, any physical or chemical interference, such as a surgical sympathectomy (a cut or clamp of a deep nerve that runs up and down along the spine) or effects of sympathomimetic drugs (stimulant compounds which mimic the endogenous agonists effects of the sympathetic nervous system) whose action is directly or indirectly linked to nervous control may result in alterations and/or damage to male reproduction, with emphasis on testicular impairment.

This present study consists of a review of data about the effects of physical or chemical alterations on the autonomous innervation and its repercussions on male gonad. For this, will be discussed the general aspect of the nervous and reproductive systems and the male gonad innervation, as well as the action of drugs or any methods that promote changes in the communication between these two systems, impairing the male sperm production and fertility.

2. Morphological description of the central and peripheral nervous system

The CNS consists of the brain and spinal cord, which are located in the skull and vertebral column, respectively [2]. The main function of this system is to process the afferent information coming from nerve stimuli into appropriate mental and motor responses in order to maintain organism homeostasis [2, 7, 14].

The PNS is made up of ganglia, nerves and nerve endings, all of which are located outside the CNS. Ganglia are characterized by a group of neuron cell bodies; nerves are structures formed by extensions of several neurons (nerve fibers), usually axons, united by a sheath of connective tissue that connect body parts and their receptors to the CNS; and the nerve endings are the terminal regions of the nerve cells, responsible for the transmission of the nervous impulse, and may be afferent or efferent [1, 2, 14]. The PNS includes 12 cranial nerves, with 10 nerves originating from the brainstem and 31 spinal nerves pairs coming from the spinal cord [1, 2].

Functionally, the PNS can be divided into an afferent (sensory) component and an efferent (motor) component. The afferent component is made up of somatic and visceral sensory nerve cells, which carry nerve impulses to the CNS from receptors distributed throughout the body and in the viscera, respectively. On the other hand, the efferent component is divided into somatic nervous system and autonomic nervous system [1, 2].

The autonomic nervous system is composed of visceral motor nerve cells, whose control is unconscious and transmits impulses from the CNS to cardiac striated muscle, smooth muscle and glands. This system can be functionally divided into sympathetic and parasympathetic autonomic nervous system [1, 2].

The autonomic nervous system (ANS) is a system of nerves and ganglia concerned with the distribution of nerve impulses to cardiac striated muscle, smooth muscle and glands. However, it is also responsible for receiving afferent impulses from these parts of the body [14]. In general, its function is to maintain the body's homeostasis, regulating digestion, body temperature, cardiovascular system, metabolism, among other vital activities. This system is divided into sympathetic and parasympathetic autonomous nervous system [3] according to its anatomical, physiological and pharmacological characteristics [1, 2].

Unlike the somatic nervous system, which needs only one neuron to transmit the nerve impulse to the effector organ (somatic motor neuron), the autonomic nervous system needs two neurons: pre- and post-ganglionic. The preganglionic neuron, whose cell body remains in the CNS, sends its axon to transmit the impulse to the postganglionic neuron, located outside the CNS in a group or collection of nerve cells called ganglia [2, 3].

Nerve impulses transmitted by fibers of the autonomic nervous system are mediated by neurotransmitters. Preganglionic fibers from both, the sympathetic and parasympathetic ANS, release the neurotransmitter acetylcholine. Postganglionic fibers, however, differ in cholinergic fibers, which release acetylcholine, and adrenergic fibers, which release noradrenaline [2].

Acetylcholine released by nerve fibers leaving the CNS acts on nicotinic receptors on postganglionic nerve fibers, just as acetylcholine released from parasympathetic postganglionic nerve fibers acts on muscarinic membrane receptors. On the other hand, noradrenaline, a neurotransmitter released by sympathetic postganglionic nerve fibers, can act on α- or β-adrenergic receptors [3]. Most organs, with few exceptions, such as the organs of the male genital system, receive sympathetic and parasympathetic innervation from various ganglia and plexuses, performing opposite functions [10].

3. The morphophysiology of the male gonad

The testis is an organ of the male genital system that can be structurally and functionally divided into two parts: seminiferous tubules and interstitium, responsible for the production of spermatozoa (spermatogenesis) and steroid hormones (steridogenesis), respectively [5, 6].

This organ is surrounded by a resistant capsule of fibrous tissue, tunica albuginea, which comprises an outer layer of visceral peritoneum made up of mesothelial cells and an inner layer of fibroblasts, collagen fibers and smooth muscle cells [10, 15].

The seminiferous tubules contain three characteristic cell types: germ cells and two types of somatic cells: Sertoli cells and myoid cells [5].

The organization of the seminiferous epithelium demonstrates that spermatogenesis is a cyclical process [16]. This process is continuous, in which diploid unipotent germ cells differentiate, and subsequently undergo the process of meiotic cell division, forming specialized haploid cells, the spermatozoa [17].

Sertoli cells play a crucial role in testis formation and in the process of spermatogenesis. Presenting in the form of syncytium, Sertoli cells assist in the progression

of germ cells to spermatozoa. In addition to keeping the seminiferous epithelium compartmentalized and intact, these cells produce testicular fluid, which is important for maintaining sperm viability, and ensure the nutrition of germ cells. They are also the main constituents of the Sertoli cell barrier, which protects the germ cells from a possible autoimmune reaction and from many toxic substances that can come into contact with the gonad via circulation [5, 15, 18].

Myoid cells or peritubular cells are cells that participate in the slow and rhythmic contractile process of the seminiferous tubules, helping to move sperm and testicular fluid [15].

The interstitium, located between the seminiferous tubules, is composed of blood vessels, lymphatics, nerves, macrophages, and Leydig cells [15]. These cells are responsible for the process of steroidogenesis, being the major source of androgens, mainly testosterone, a hormone produced from cholesterol [19].

4. Autonomous sympathetic and parasympathetic innervation of the male gonad

The testicle (**Figure 1**) receives autonomous innervation mainly into the superior and inferior poles [20, 21] specifically by the superior and inferior spermatic nerves, which reach this target organ by two different paths: the superior spermatic nerves originate from the superior mesenteric ganglion (rostral) reaching the gonad by testicular artery; and the inferior spermatic nerves originate from the inferior (caudal) mesentery ganglion (sympathetic fibers) and the pelvic nerves (parasympathetic fibers) that accompanies the vas deferens and penetrates the testis through the inferior pole [22–24]. In some species, there is a possible route directly from the hypogastric nerves into the inferior pole or it may converge on the inferior spermatic nerve itself, such as the mammal *Suncus murinus* [20].

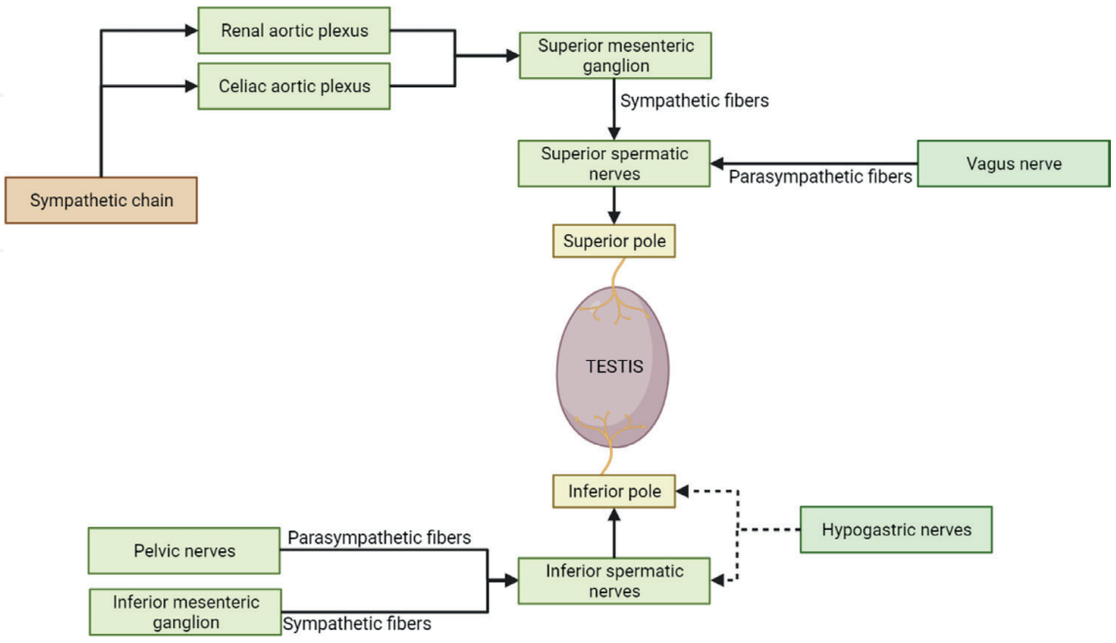

Figure 1.
Schematic drawing of the autonomic sympathetic and parasympathetic innervation that are directly involved in the nervous control of the male gonad of many animal models.

The superior spermatic nerve, the major contributor to testicular innervation, originates from the superior mesenteric ganglion which receives fibers via the celiac and renal aortic plexuses, running along the testicular vessels. The sympathetic component comes via the intermesenteric nerves, and the parasympathetic component of the spermatic nerve via the vagus nerve. These superior spermatic nerves are peculiar, as they are the only nerves that come directly into contact with the testis, without communicating with other groups of nerves [25–27].

It is known that the inferior spermatic nerve may contain both sympathetic and parasympathetic fibers, which exert their functions by activating specific membrane receptors [10]. Within the testes, both nerves are distributed in stromal compartments, the tunica albuginea, the mediastinum, and the perivascular tissue [10].

5. Role of autonomous innervation in the male gonad

The autonomous innervation of male gonads plays a fundamental role in the control of testicular blood flow, via nervous stimuli to the blood vessels contractile cells, thus ensuring the circulation of hormones coming from the hypothalamic-pituitary-gonadal axis and testicular temperature control, a factor that guarantees the survival of germ cells [13, 28–31].

Several studies have shown that changes in the autonomous innervation of the gonads play direct or indirect effects on the spermatogenesis process [27, 32–34]. Studies regarding testicular denervation via spermatic nerves have shown a reduction in the number of spermatids and an increase in germ cells undergoing apoptosis [34]. Huo et al. [35] found that, after denervation of the superior and inferior spermatic nerves during puberty, the autonomic innervation plays a fundamental role in the development of the seminiferous tubules and in the initiation of spermatogenesis.

On the other hand, stimulation of the superior and inferior spermatic nerves could also promote changes in spermatogenesis. Nudmamud-Thanoi et al. [36] showed that a synthetic CNS and PNS stimulant drug (methamphetamine) induces apoptosis in seminiferous tubules and affect sperm quality directly by the reduction of progesterone receptor (PR), estradiol receptor α (ERα) and β (ERβ) expressions in male germ cells and Sertoli cells.

In fact, the somatic cells also play a crucial role during the spermatogenesis process. Leydig cells are responsible for the process of steroidogenesis, being the major source of androgens, mainly testosterone [19].

Autonomous innervation via the superior spermatic nerve is related to the expression of LH (luteinizing hormone) receptors in Leydig cells of immature rats, ensuring the testicular development of these animals [34]. Other receptors also expressed on Leydig cells are adrenoceptors. Favaretto et al. [37] demonstrated, in Leydig cell culture, that these cells express subtypes of adrenoceptors in their membrane and, according to the specific activation of these receptors, there is inhibition (activation of the α2-adrenoceptor) or stimulation (activation of the β2-adrenoceptor) of testosterone secretion.

Later, studies carried out by Gong et al. [38] suggested that the expression of adrenoceptors in Leydig cells provided, via autonomous innervation, a fine control of the functioning and survival of these cells. Previous studies carried out by Frankel and Ryan [39] demonstrated for the first time in rats that the innervation of the testis was necessary to produce an increase in the plasmatic level of testosterone under stress. This physiological action aimed at controlling hormone secretion in the gonads via autonomous innervation was confirmed by Chiocchio et al. [40] and Gerendai et al. [25].

Chiocchio et al. [40] observed that the role of innervation on testosterone secretion via Leydig cells occurs strictly by stimulation of the superior spermatic nerve. The inferior spermatic nerve performs only a vasodilator action, facilitating the circulation of the hormone. However, Sosa et al. [23] demonstrated that when stimulating the inferior spermatic nerve, via noradrenaline, there was an increase in the concentration of testosterone in the testes.

An ex vivo experiment, Cavicchia et al. [41] demonstrated that by stimulating both the superior mesenteric ganglion and the inferior mesenteric ganglion, the nervous stimuli generated on adrenoceptors on the testes promoted an increase in the release of androstenedione, as well as an increase in the release of noradrenaline by nerve fibers. This result corroborates previous studies, demonstrating that both ganglia, superior and inferior, are directly involved in the production and release of testosterone, since the noradrenaline release acts on the adrenoceptors present in the Leydig cells.

Although it is known that both sympathetic and parasympathetic fibers innervate the testes, few studies demonstrate the role of cholinergic innervation in this gonad. Zhu et al. [42] demonstrated that acetylcholine, via parasympathetic innervation coming from the inferior spermatic nerve, exerts an inhibitory effect on testosterone secretion, suggesting its participation as a modulating agent in the release of this hormone.

However, it is not only with the regulation of testosterone secretion and in the process of spermatogenesis in adult rats that testicular autonomic innervation is related [35]. Rosa-e-Silva et al. [43] by promoting chemical sympathectomy of the autonomic nervous system in prepubertal rats using guanethidine, demonstrated that the autonomic innervation is involved in the androgen biosynthesis responsible for the transition from immature rats to sexually mature rats.

Later, Lamano-Carvalho et al. [44] following the same line, demonstrated that, after chemical sympathectomy, prepubertal animals presented an increase in the concentration of progesterone and a decrease in androstenedione and testosterone levels. Knowing that progesterone is converted into androgens, these results showed that the sympathectomy possibly promoted a blockade in the steroidogenic enzymatic process, inhibiting the action of the enzymes 17α hydroxylase/17,20 desmolase.

Spermatogenesis, on the other hand, is not modulated by testicular innervation alone. It was observed that germ cells and Sertoli cells express receptors and mRNA for acetylcholine, demonstrating that a non-neuronal cholinergic system also plays a role in the germ cell differentiation process [45].

In addition, autonomic innervation also exerts effects on the testicular parenchyma. It was observed alterations in the volume and weight of the gonads submitted to chemical denervation process [46]. However, Zhu et al. [42] in an experiment carried out with the aim of mapping the nerves that reach the gonad, did not obtain results that attest to the presence of innervation in the testicular parenchyma.

The tunica albuginea, the fibrous tissue that lines the testes, also plays a role during spermatogenesis. It is known that contraction of the muscularis layer of the tunica albuginea associated with contraction of the seminiferous tubules via myoid cells may be responsible for transporting sperm from the seminiferous tubules to the caput of the epididymis [47, 48].

Banks et al. [49] observed some differences between the action of neurotransmitters noradrenaline and acetylcholine in a study demonstrating the role of neurotransmitters in different species (human, rat, rabbit and mouse) on the smooth muscle cells contraction of tunica albuginea. Acetylcholine did not produce muscle contraction in humans, and in mice noradrenaline promoted muscle cell relaxation.

The nerve fibers that reach the smooth muscle cells of the tunica albuginea have different characteristics between species. In humans, these nerve fibers are in contact, via synapse, with all muscle cells [49]. On the other hand, the action potential transmission in rats and rabbits occurs through gap junctions between cells, demonstrating that the fibers reach only the superficial cells of the muscular layer [49].

The nerve fibers that reach the gonads, besides promoting crucial stimuli for testosterone production and during spermatogenesis, are responsible for the degenerative process of the testes in animals that have undergone vasectomy [50].

Recently, several studies have related the use of sympathomimetic drugs or neurotransmitter reuptake inhibitor drugs with spermatogenesis problems. Studies on the direct effects of illicit drugs (CNS and PNS stimulants or depressants) on the male reproductive system described damage caused to the gonad, mainly after exposure to amphetamines, cocaine, opioids, and marijuana [51]. This review suggested that taking all kinds of illicit drugs can result in subfertility or complete infertility in the consumers. It described Leydig cells dysfunction and also structural alterations of seminiferous tubules.

Venlafaxine, a norepinephrine and serotonin reuptake inhibitor, impairs rat spermatogenesis and causes high intratesticular levels of estrogen and testosterone [52, 53]. Moreover, sibutramine, another serotonin-norepinephrine reuptake inhibitor, promoted androgen depletion in long-term exposed male rats [54, 55]. These effects further highlight the sympathetic nervous control over the steroidogenic activity of Leydig cells and the importance of innervation in the male gonads.

Therefore, the autonomous innervation of testis corresponds to an important axis in the control of the spermatogenesis process and on the transport of spermatozoa to the caput of the epididymis, being crucial for the maintenance of the structure and function of the male gonad (**Figure 2**).

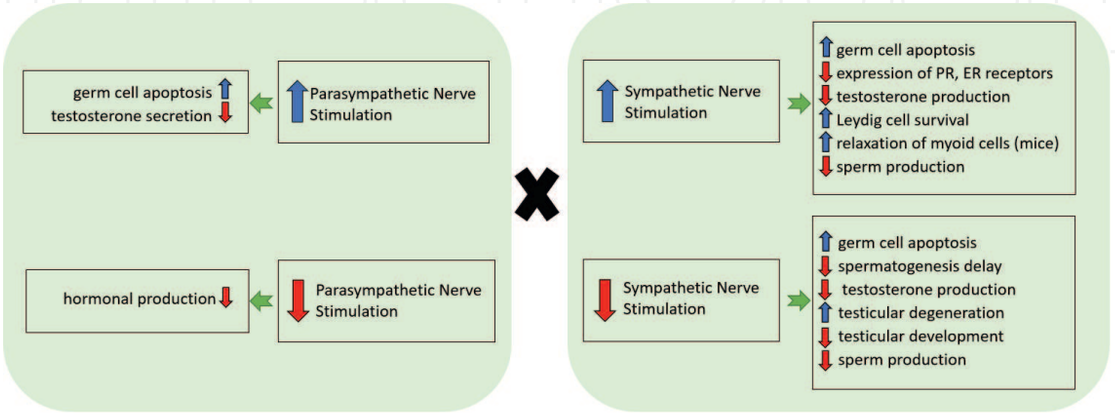

Figure 2.
Schematic drawing of the role of autonomic sympathetic and parasympathetic innervation on male gonad.

6. Conclusions

The internal male genital system is innervated by a fine and complex nervous structure, in which the control performed by the CNS is directed by sympathetic and parasympathetic ANS [10]. Adrenergic and cholinergic fibers play key roles in maintaining the functional and structural integrity of the organs that compound the male genital system [7–9, 11, 14].

Studies carried out so far demonstrate that the total absence or partial interruption of nervous communication with the testis causes effects from structural alterations to problems in male fertility, as reduction on sperm production, sperm delivery to the epididymis and testicular degeneration [48–50]. On the other hand, there are few studies demonstrating the actions of sympathomimetic drugs on the male gonad. Changes in sperm production and decrease in testosterone levels, as well as decrease in sperm fertility have been reported during the effect of these α-adrenergic agonist drugs [41, 47–49].

Thus, more and more studies must be carried out as the pharmaceutical industry releases new drugs that may directly or indirectly act on the autonomous innervation of the testis, bringing new knowledge and possibilities for therapies or minimizing long-term impacts after harmful exposures.

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Conflict of interest

The authors declare no conflict of interest.

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