RESEARCH ARTICLE

A pelvic trinity: prostate, hormones and nerves

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Abstract

The prostate is an accessory sex gland responsible for producing and excreting prostate fluid. In the male rat, hormones such as testosterone (T) and prolactin (PRL) and the pelvic and hypogastric nerves regulate the gland, providing afferent information and adrenergic and cholinergic innervation to the prostate. Damages in the innervation or alterations in the hormonal levels of T and PRL changes the prostate's cytoarchitecture and function that can promote the presence of cancer. However, sexual activity delays effects induced by hormonal alterations or dysfunction of the autonomic nervous system, but it does not mean that they do not appear since the cases of death from prostate cancer is still increasing. That is why this review has the fundamental purpose of showing the relationship between the hormones, autonomic nervous system, and sexual behavior in the pathophysiology of the prostate, with the ultimate aim of trying to understand the role that each one plays in diseases of the prostate. To date, results show that morphological changes in the prostate correlate with an increase in prolactin serum levels, a decrease in androgen and long prolactin receptors, and an increase in short prolactin receptors. Also, damage in the innervation induces an increase in androgen and muscarinic receptors in the major pelvic ganglia that supply the nerves that control the prostate in animal with sexual experience.

Key words: prostate, hormones, major pelvic ganglion, sexual behavior

1. Introduction

The male reproductive system is a complex structure of external and internal organs, such as accessory glands like seminal vesicles, coagulant glands, and the prostate.[1] The latter is responsible for producing and secreting prostatic fluid, a substance that plays an essential role in reproduction because it guarantees fertilization and reproductive success and its function is impacted by sexual behavior .[2–4] The prostate gland is regulated by steroid hormones such as T and estradiol and proteic hormones such as PRL, among others; in addition, nerve fibers from the major pelvic ganglion (MPG), attached to the lateral portion of the prostate, also reach this gland.[5] In turn, this ganglion receives nerve fibers from the viscerocutaneous branch of the pelvic nerve (NPv) that comes from the lumbosacral segments (L6 and S1) of the spinal cord and from the hypogastric nerve (NHg), which originates from the inferior mesenteric ganglion that receives fibers emerging from thoracolumbar segments (T13, L1, L2).[5–7] The exact role of innervation to the prostate is unknown, but some studies indicate that gangliectomy (the complete removal of the ganglion) or damage to the NPv and NHg nerves induce histological changes in the prostate tissue. Therefore it is inferred that it controls the cytoarchitecture of the gland, possibly by promoting the release and participation of trophic factors related to the maturation and differentiation of epithelial cells.[8,9] For this reason, it is essential to maintain the homeostatic balance between the nerves and the prostate because any alteration could cause the appearance of various diseases in the gland.[2,3] It is important to mention that the prostate and MPG respond to the execution of sexual behavior by increasing the area of both structures and the expression of receptors. However, the interaction of these two systems in a physiological way is still unknown and even less under pathological conditions. The first results indicate that morphological changes in the prostate is a consequence of the increase in PRL serum levels and decrease of androgen and short PRL receptors and increase in long prolactin receptors in the prostate, but also changes in the innervation plays a critical role in generating invasion and metastasis where the classic neurotransmitters (acetylcholine and adrenaline) are essential. In this sense, an increase in androgen and muscarinic receptors occurs in the major pelvic ganglia responsible for innervating the prostate. Regardless of this, many questions remain regarding how ANS, the endocrine system, the immune system, and sexual behavior are associated with prostate pathophysiology. For this reason, this review aims to present advances on the relationship between nerves, hormones, and sexual behavior concerning the physio-pathogenesis of the prostate.

2. Prostatic Gland

2.1Anatomy

The prostate is an accessory gland that belongs to the male reproductive system and is present in all mammalian species. Before describing the anatomy of the prostate, the first thing we must know is the origin of the word. Marx and Karenberg (2009) mention that the word prostate has its origin from the Greek "prostates", composed of the prefix pro (= before), the stem sta (stand), and the suffix tes (which forms a general pronoun). It literally means "something that stands before someone or something",[11] but it is also known as the “guardian” or “protector”.[12] Regardless, the prostate is a gland that is part of the male reproductive system that plays an essential role in reproduction. The anatomical description of the human prostate dates from 1868, reported that it exhibits lobes that were called anterior, lateral, posterior, and medial, with the lateral lobes forming

the main portion of the gland.[13] The Sixth International Nomina Anatomica (IANC, 1989) recognizes them as base, apex, right, left, middle lobes, and isthmus. Clinically, McNeal (1988) divides the prostate into "zones". This description begins at the site where the urethra changes direction (35º), corresponding to the distal urethra, known as vomeromontanum. The prostatic utricle and the ejaculatory ducts converge in this region, which McNeal (1968) calls coronal.[14,15] The central zone is on each side of this region that constitutes 25% of the prostate, more laterally is the peripheral zone that makes up 70% of the entire gland, while the transition zone starts from the preprostatic sphincter, it ends in the peripheral zone and constitutes 5% of the glandular prostate.[14] In humans, the prostate is a compact mass, where a septum delimits the areas and the zones are not visible, making it difficult to distinguish them; the opposite occurs in other mammals, for example, the rat, where its identification is easy.[13,14,16] Thus, the anatomical concept of the prostate by zones was established, using the verumontanum as a base reference.[17] The central zone was specified as a wedge of glandular tissue surrounding the ejaculatory ducts, the peripheral zone extends caudally towards the distal part of the urethra, and the transition zone corresponds to the portion of the prostate surrounding the urethra.[17] In rodents, the prostate is mainly described by "lobes", because a thin mesothelial membrane separates each lobe that facilitates its visualization, and are called the lobe or ventral prostate (PV), lobe or dorsal prostate (PD), and lobe or lateral prostate (PL); the latter two are called the lobe or dorsolateral prostate (PDL).[18–20] The alveoli of the rat PDL have an arrangement like the peripheral zone in humans, and therefore it is compared to the human prostate.[21,22] However, the PV of rodents does not have a region comparable to that of humans because its stroma is a fibromuscular type, and its function is different.[18,19]

2.2 Histology

Regardless of the anatomical differences of the prostate between humans and rodents, there are histological similarities that allow the use of rodents as a model to study prostate function and the generation of diseases.[13] Histologically, the prostate is composed of acini or alveoli and ducts that connect with the prostatic urethra, and in both humans and rats, the alveoli are composed of epithelial, basal, and neuroendocrine cells, surrounded by the stroma.[20] In the human prostate, the epithelial cells have some differences depending on the area. The nuclei are long, pale, and located at different levels in a granular cytoplasm in the central zone. In contrast, in the peripheral zone, the cells are columnar and polar because they have an apical zone (directed towards the lumen) and a basal zone (directed towards the stroma), the nucleus is round, dark, and located in the basal area, and the cytoplasm has a pale eosinophilic coloration.[13,14] Basal cells are adjacent to the basal membrane and have an elongated nucleus. Their number can vary between each alveolus; however, neuroendocrine cells are not easy to identify using hematoxylin and eosin (HE) staining, but markers such as chromogranin or synaptophysin allow their observation.[18] The stroma is abundant and contains fibroblasts, blood vessels, nerve fibers, and a large amount of smooth muscle.[19] On the other hand, the prostate of rodents (rat and mouse) also contains alveoli, ducts, and a stroma like the human prostate, except that the epithelial cells are columnar in VP and cuboidal in DLP.[20] Similarly, basal cells are adjacent to the basement membrane; also neuroendocrine cells, although in less quantity than in humans.[23] The stroma is more abundant in

the PDL than in the PV, containing the fibroblasts, blood vessels, nerve fibers from the pelvic and hypogastric nerves, and smooth muscle surrounding the alveoli and the ducts.[24]

2.3 Function

The prostate is an accessory gland of the male reproductive system, and its primary function is to produce the prostatic fluid necessary for the fertilization of the ovum. Considering that it is part of the male reproductive system, the execution of sexual behavior impacts its function and histological characteristics. Various mechanisms become active during the sexual performance, converging on the prostate to expel prostate fluid during ejaculation. During sexual arousal, the afferent stimuli perceived in the pelvic area, the eyes, and the ear converge in the medial preoptic area and the arcuate nucleus, located in the hypothalamus, which maintains this state of arousal and induces prolactin secretion (PRL) and testosterone by the testis.[2,25] These hormones increase in the blood and bind to receptors located both in the testicle and in the prostate to complete sperm maturation and the production of prostate fluid that constitutes approximately one-third of the total ejaculated volume. Thus, seminal or ejaculate plasma comprises sperm from the testis and secretions from the seminal vesicles (for example, the seminogelin), the cooper's glands (for example, glycoprotein mucin 1 or MG1), and the prostate.[26] Prostatic fluid is a milky substance with alkaline properties that neutralize the acid secretions generated by the vagina, allowing sperm mobility and survival.[17,27] This liquid contains zinc, citric acid, acid phosphatase, prostaglandins, seminin, spermine, spermidine, cholesterol, aminopeptidases, plasminogen activator, fructose, dorsal proteins I and II, and proteolytic enzymes such as kallikreins 1 and 3, also known as prostate specific antigen (PSA), and cathepsin D. PSA and cathepsin D not only promote the liquefaction of semen and therefore the release of sperm, but also induce the production of VEGF-C and VEGF-D, proteins that are also an essential component of seminal fluid[4,28]; distant sexual stimulation or its execution increases the levels of cathepsin D in the prostate.[29] Thus, all these components are not only essential to guarantee the survival of sperm in the female's uterine tract, but they also participate in sperm capacitation and activation.[2,3,30]

3. Endocrine regulation of the prostate

Considering that the prostate is a gland that belongs to the male reproductive system, it is not surprising that steroid hormones control its function, mainly by T. However, it is imperative to mention that the luteinizing hormone, estradiol, PRL, the vasoactive intestinal peptide (VIP) and substance P are also involved in the control of prostate function. Notwithstanding, hormonal participation in the gland is poorly known because research has been focused mainly on the effects of androgens and, recently, PRL because both hormones participate in the synthesis of prostate fluid and the generation of prostate diseases.[31]

Prostate function is regulated mainly by T and its metabolite dihydrotestosterone (DHT), which is biotransformed in the prostate stroma by the action of the enzyme 5α-reductase and hormones such as prolactin (PRL).[32–34] Androgens, particularly DHT, are essential for the maintenance and function of prostate tissue since, during prenatal development, the production of DHT is necessary to complete the morphogenesis, differentiation, and maturation of the prostate, an event resulting from its union with the RA.[35] During this phase, the formation of the alveoli requires the action of this hormone.

However, the epithelial cells do not express RA; hence it is proposed that growth factors regulated by androgens are responsible for promoting the development of the gland.[36] At the end of fetal development or immediately after birth, T secretion begins, and at this moment, androgens take importance in development and function in the gland because they regulate gene expression related to this event.[37] As the individual's development progresses, androgens maintain both the balance between apoptosis and proliferation that ranges between 1-2%,[37] and the paracrine and autocrine communication between glandular and stromal cells to produce transcription factors such as Hoxa13 and Hoxd13 and bind to specific regions of DNA that are critical in the development of the reproductive system.[30,38] Thus, T presence is of significant importance because its absence reduces the weight of the prostate due to the loss of 70% of glandular epithelial cells by apoptosis. This effect causes a delay in the differentiation of these cells due to down-regulation of the Wnt family and Bmps/Tgfb/activin affecting the organization of the prostate epithelium and consequently its function by decreasing the production of prostate fluid.[38–40]

In resting conditions, the serum levels of testosterone oscillate between 3ng/ml and prolactin in 10ng/ml, and these levels are sufficient to maintain a balance between the weight and the histological characteristics of the gland and the production of the prostatic fluid. Otherwise, during sexual activity, the physiological conditions change substantially. During copulation, pheromones from the female stimulate the nasal epithelium and the vomeronasal organ in the male. This information is recorded and sent to brain areas such as the corticomedial amygdala and the medial preoptic area of the hypothalamus that controls sexual behavior.[41,42] This information also converges in the paraventricular nucleus of the hypothalamus. This structure communicates with the pituitary gland to promote the release of luteinizing hormone and increase PRL levels in the blood to induce testosterone synthesis in the testicle, which is associated with increased androgen and prolactin receptors in the prostate.[2,43,44] In addition to this, the consistent execution of sexual behavior increases the volume and weight of the prostate, alveolar area, and epithelial height and the demand for prostatic fluid synthesis. For this, both hormones participate by capturing zinc, producing citrate, PSA and inducing a significant increase in cathepsin D.[17,25,29,45] The direct importance of all this is that the components of seminal plasma participate in events that are key in the function of sperm and fertilization, one of them is the liquefaction of seminal plasma. The other is sperm capacitation and activation.[30,46] On the other hand, prolactin performs many functions as those related to reproduction mentioned above.[47] Although the function of this hormone in prostate regulation is poorly known, it participates in the development, growth, and maturation of the prostate and the survival and proliferation of epithelial cells.[48–51] This hormone, together with androgens, regulates the expression of mitochondrial enzymes such as aspartate aminotransferase, pyruvate dehydrogenase, and mitochondrial aconitase, necessary for the production of citrate.[48,52] Zinc also regulated citrate production by epithelial cells, and the prostate contains high levels of this compound, where androgens and PRL are involved in its capture.[53] The presence of this mineral in the gland is significant since it regulates cellular metabolism, and the importance of having high levels of zinc within the mitochondria is because this mineral inhibits the activity of the enzyme

aconitase and therefore the oxidation of the citrate, maintaining the energy levels required for an adequate metabolism.[54–56] Conversely, hyperprolactinemia (high and sustained levels of prolactin in the blood), exert the opposite effect, decreasing the quality of semen and the quantity of sperm because of high levels of citrate, and something similar occurs when the levels of T decrease.[34,57–59]

4. Participation of T and PRL in the generation of diseases in the prostate

Benign prostatic hyperplasia (PBH) and cancer are diseases with the highest incidence, but how these diseases develop is still unknown. The origin of these prostate diseases seems to be the genetic load, the environment, and the lifestyle. Despite this fact, what is not conclusive is the participation of the hormonal system. As mentioned above, testosterone and PRL are two hormones known to regulate the gland's function and the generation of diseases in the prostate. For this reason, the drugs developed, to date, mainly include its actions on testosterone, but it is not the only system responsible for this. Benign prostatic hyperplasia (BHP), as its name indicates, is a non-critical development because of an increase in the number of cells as a consequence of an increment in the rate of cell proliferation. Of course, its incidence is related to age; at 40 years, the BHP presence is about 20%, at 60 years is 70%, and after 80 years it increases up to 90%.[60] BPH is a benign growth that does not affect the person's life, although prostate volume increases depending on cell proliferation. Hence, grade I is when the volume is less than 50 cc, grade II reaches 100 cc, and grade III when the size exceeds 100 cc.[61] BPH frequently develops in the transition zone, which is the site that surrounds the urethra and can oppress it generating pain, bleeding resistance to the emptying of the bladder, and urine retention, which over time can generate recurrent bladder infections.[62] Although it is unknown what induces the development of BPH, it is proposed that androgens, mainly DHT, a metabolite produced in the gland, are responsible for the appearance of this disease. A reason proposed of why HPB develops mainly in the transition zone is because of steroidogenic capacity. Although in the transition (TZ) and the peripheral zone (PZ), the steroidogenic capacity is similar, the difference between them is the way using the steroidogenic precursors.[63] Of course, more research is required to determine if DHT is the only hormone involved in developing prostate disease and probably explain why anti-steroidal procedures are not always successful. The presence of diseases in the prostate and its development are still unknown because of the complexity of the molecular processes involved. However, both high and low serum testosterone levels are responsible for inducing prostatic diseases, yet advancing age is more related to low systemic levels of testosterone[64] and increased levels of PRL, and both hormones promote diseases in the prostate.[24] What is a fact is that the therapies used to prevent testosterone's actions do not consider the participation of PRL.

Regardless of this, an obligatory question is why some individuals generate hyperplasia and others cancer? The answer is not yet known, but as mentioned, both PRL and T promote the onset of prostate diseases. BPH and cancer outcomes include an enlarged prostate due to PRL-induced cell proliferation and survival induced by binding to a receptor belonging to the cytokine superfamily 1. One result of this is because PRL activates intracellular signaling pathways such as JAK-STAT kinases (signal transducers and activators of transcription) and MAPK (mitogen-activated protein kinases).[27,65–68] Since 1955, it has been reported that PRL is

necessary for the development and maturation of the gland because its absence during embryonic development induces prostate atrophy in adulthood.[69] However, the chronic administration of PRL and T in adult rats induces the appearance of precancerous lesions in the prostate gland, showing that alteration in the homeostasis of these hormones is responsible for prostatic hyperplasia and cancer.[31] The mechanisms involved in these diseases are complex and multifactorial since they involve the loss of hormonal balance and signaling pathways and involve a decrease in zinc uptake by epithelial cells. Consequently, the aconitase enzyme remains activated, producing constant oxidation of citrate and production of the energy required by diseased cells to proliferate and survive and maintain the progress of the disease.[56] The severity of the disease implies that cells proliferate and lose their shape due to the loss of unions between cells, along with cytoskeleton and extracellular matrix degradation. Then, the cells acquire the ability to migrate to other sites within the tissue or outside of it (metastasis). PRL regulates the expression of cadherin that maintains this union and becomes a marker that indicates the aggressiveness of the disease in prostate tissue.[70] The role of PRL in the induction of diseases in the prostate is more critical when cancer becomes resistant to androgenic action. In older men, the stage in which the appearance of prostate pathologies begins, T levels decrease, and PRL increases.[71,72] It is necessary to consider that the effects of PRL do not necessarily require that they remain constantly elevated because the transient increases also induce histological changes in the prostate without affecting the performance of sexual behavior. Regardless of whether PRL remains constantly elevated or not, both conditions increase the expression of the short receptor, which indicates that the lesions present in the prostate appear to be the product of the increase in this receptor. Its importance is because this receptor participates in the regulation of cell proliferation.[25,73] Although it deserves more studies in this regard, it is possible to consider the increase in this type of receptor as a trigger for prostate lesions.

5. Autonomic regulation

The autonomic nervous system (ANS) is divided into the sympathetic and parasympathetic complex, originates in the medulla oblongata, and consists of two chains of 23 ganglia distributed along the spinal cord to innervate different peripheral organs. It is a fundamental neurovegetative structure because it transmits information from the spinal cord to the brain, and vice versa, to regulate involuntary functions such as the secretion of gastric juices and control reflexes such as coughing and vomiting, sneezing, swallowing, among others.[74] Anatomically, it is divided into segments: a) cervical region, which controls light uptake, secretion of pituitary hormones, swallowing, heartbeat, and thyroid function; b) thoracic region, which supplies organs such as the lungs and the heart; c) lumbar region, where they have a connection with most of the intra-abdominal organs, such as the spleen, liver, diaphragm, and stomach; and finally d) pelvic region, formed by two chains of ganglia that connect with the coccygeal ganglion, and is the area of the sacral plexus, also known as the pelvic plexus in humans or the major pelvic ganglion (MPG) in the rat, whose function is to control various pelvic organs such as the rectum, bladder, seminal vesicles, penis, and prostate.[1,31,75,76] MPG is part of the ANS and innervates the prostate; in the male rat, it is attached to the DLP and has a pyramidal shape. An adult animal's dimensions are 2 mm wide by 4 mm long,

and the neurons become innervated by preganglionic fibers from the PvN and HgN nerves.[3,5,74,77] HgN is very characteristic because it emerges from the inferior mesenteric ganglion, which receives fibers from the thoracic T13 and lumbar spinal segments L1 and L2; it contains about 1600 fibers carry afferent, sympathetic and parasympathetic information.[74] On the other hand, the PvN originates from the lumbar L6 and sacral S1 segments carrying about 5000 axons. It divides into the somatomotor branch, innervating the iliococcygeal and pubococcygeal muscles, and the viscerocutaneous branch, supplying the MPG. Similar to the HgN, it conducts afferent, sympathetic, and parasympathetic information.[1,74,78] The MPG in adult males contains about 11,900 neurons, with a 15 to 40 µm diameter and a soma area between 100 and 1300 µm².[5,7,79] Also has SIF cells (small intensely fluorescent) classified as type I, a dopaminergic cell considered an interneuron, and type II, a neuroendocrine cell containing small vesicles in its cytoplasm. There are also the Schwann cells that form myelin, endothelial cells, and satellite cells, which surround neurons and control the neuronal microenvironment and synaptic transmission.[80,81] It has also been reported that both neurons and SIF cells in the MPG express receptors to acetylcholine, epinephrine, androgens, GABA A, purinergic, and endocannabinoids.[77,82,83] It has been described that neurons in the ganglion are distributed in specific regions, depending on the target organ they innervate.[3] In this way, it was possible to determine that the neurons innervating the colon are in the dorsal region, near the entry site of the NPv and NHg nerves. The neurons innervating the penis are in the dorso-caudal region, where the cavernous nerve responsible for the erection originates. The neuronal bodies that control the bladder exist throughout the ganglion (ventral, dorsal, caudal, and rostral). In contrast, the neurons that regulate PV exist only in the ganglion's ventro-caudal region, which corresponds to the site where the prostatic or accessory nerves originate.[3]

5.1 Autonomic innervation of the prostate in the male rat

The ANS plays an essential role in the prostate gland's growth, maturation, and secretory function because the prostate receives sympathetic, parasympathetic, and afferent fibers from the MPG.[3,6,20,83] The most afferent information of the rat prostate originates from the dorsal root ganglia at the level of the L6 (40%) and L5 (20%) segments.[84] Concerning adrenergic and cholinergic innervation, the distribution of these fibers in the prostate is unknown, but they participate in the contraction of the smooth muscle that surrounds the ducts and the epithelial cells of the alveoli.[27] Both lobes contain both sympathetic and parasympathetic fibers, but the proportion is different in each of them; the PV has a higher proportion of adrenergic type fibers, while the PDL has a similar density of both fibers.[85] Although epithelial cells contain fibers from MPG, the role in the synthesis of prostatic fluid is still unknown; but, some studies indicate that this system contributes to regulating cell proliferation and promoting metastasis in prostate cancer.[86] To date, the mechanisms used by ANS to promote the development of diseases in the prostate are not precisely known, but it seems that the hyperactivity of this system is one of the factors that trigger the development of the pathologies reported in the gland.[86] In humans, approximately 50% of invasive cancers develop by hyperactivity of the nerves located in the gland, suggesting that the sympathetic nervous system favors prostate tumors, principally in its early stages where the activation of adrenergic receptors (β2 and β3) are involved. In contrast, the

parasympathetic nervous system participates promoting metastasis by activating M1 muscarinic type receptors.[27,84]

Although the prostate receptors activated to initiate diseases are known, the exact molecular mechanisms involved in tumor growth and the ability to metastasize are still not well understood; however, in humans, it has been suggested that removal of the pelvic plexus could be used as a possible treatment, considering that in mice this procedure stops the development of the prostate tumor. However, it requires more support because the suspension of the splanchnic nerve cause dysplasia and colorectal cancer in mice.[86–91] The reason for this is still unknown, but it must be considered that the prostate has sympathetic and parasympathetic control, so both systems would have to be eliminated as a possibility to stop the progress of the disease, at least under the reported experimental conditions.

Although this hypothesis needs further analysis, it is necessary to consider that in these studies, the tumors generated in the prostate come from cell lines that were injected in the vicinity of the gland. In the tissue, they start to grow, generating a tumor accompanied by an increase in the rate of cell proliferation and irrigation and innervation that supports the development of the tumor. Thus, this condition is entirely different from the "natural" development of a disease that arises from healthy tissue.[92]

Another hypothesis establishes that the loss of innervation induces the generation of prostate pathologies, based on the fact that diseases in the prostate begin in mature adult subjects (40 years and older), a stage in which T decreases and PRL increases in the blood, along with age-associated degeneration of the nervous system.[8,93] Thus, innervation plays a significant role in the maintenance and development of the prostate since the suppression of its control by gangliectomy (removal of the PMG) or by preganglionic lesion of the PvN and HgN nerves causes various effects that include: a) histological, changes similar to prostatic hyperplasia, metaplasia or dysplasia; b) physiological, because the prostate cell gradually loses the ability to produce prostatic fluid and prevents the release of testosterone by the testicle in response to the performance of sexual behavior and, c) molecular, because the expression of RA in the gland decreases.[9,33,85,90,94] Considering the different experimental procedures and the results derived from them, studies are still needed to indicate how the ANS promotes the generation of diseases in the prostate and its relationship with the endocrine system in order to prevent their development.

6. Association between sexual behavior, GPM and prostate

During sexual stimulation, the male perceives afferent stimuli from smell, hearing, vision, and the peri-genital area that prepare him to respond to sexual activity and reproduction; this means that the motivation generated by the contact with the receptive female culminates in the execution of the sexual behavior.[95,96] In the case of the male rat, its sexual behavior comprises an ordered sequence of motor movements known as a) mounting, where the male makes contact with the female without penetrating the penis; b) intromission, which includes the insertion of the penis into the female's vagina and, finally, c) ejaculation, which involves the expulsion of semen into the uterine tract of the female.[27,84] When the male is for the first time with a receptive female, he is considered an inexperienced male, and the reason for this is not because it is the first time he has contact with the female, but also in his sexual performance, since during the execution behavior makes more mounts

than intromissions and, therefore, takes longer to ejaculate (20 minutes). As the male frequently copulates with the female, the time it takes to reach ejaculation decreases (10 minutes) because he has more intromissions and fewer mounts, and at this moment is considered sexually experienced.[41]

During copulation, pheromones from the female stimulate the nasal epithelium and the vomeronasal organ in the male, information that reaches brain areas such as the corticomedial amygdala and the middle preoptic area of the hypothalamus, which is part of the brain responsible for regulating sexual behavior.[41,42] This information also converges in the paraventricular nucleus of the hypothalamus, a structure that communicates with the pituitary to synthesize hormones such as follicle-stimulating, luteinizing, and PRL, and towards thoracic and lumbosacral segments of the spinal cord to regulate the autonomic circuits where it is involved the MPG. The information converging in this ganglion activates neurons that regulate the penile erection, the testes, and accessory glands such as the prostate, seminal vesicles, cooper or bulbourethral glands.[3] The central and autonomic events activated in response to the behavioral execution culminate with the semen expulsion, which results from the mixture of the different secretions of the glands and, together with the sperm, is deposited in the female's vagina to carry out the fertilization process.[1,41,42,95,97] Therefore, the execution of sexual behavior, in addition to involving several central and peripheral circuits, also incorporates the endocrine system and, together, promotes reproductive success.[98] This is because, during behavior, serum T and PRL levels increase, which correlates with the increase in the expression of their respective receptors in the prostate and the activation of the signaling pathways used by PRL.[99] Although it is known that these hormones are involved in the production of prostatic fluid and proliferation and survival of prostate cells,[100] the response to sexual behavior seems to involve the hormonal rather than the nervous system. The execution of sexual behavior does not impact the expression of muscarinic and adrenergic receptors, so it is possible to suppose that their participation may involve the contraction of the smooth muscle located around the ducts to promote the expulsion of the contents of the gland.[1–3,85,89,90] It is essential to mention that all these receptors are in the MPG, but none of them increase in response to sexual behavior; however, the behavior has trophic changes in the ganglion such as an increase in the area of the neural soma and the number of neurons in the ventro-caudal region (a site that regulates PV), while in the prostate the epithelial height and area alveolar increase.[87,101] These histological changes have a physiological repercussion because the ganglion-prostate system becomes efficient to respond to a behavioral event that takes place intermittently and for a long time.[101,102]

The effect is opposite when preganglionic HgN and PvN nerves become altered, since these conditions produce that the area of MPG and neurons decreases significantly, changes that correlate with the increase in the expression of muscarinic receptors and AR, leading to suggest that changes in the ganglion are also responsible for initiating prostate pathologies.[87,102] This proposal is supported because the absence of nervous control in the prostate induces histological changes similar to hyperplasia and dysplasia, both in subjects never exposed to the presence of a receptive female and in those sexually experts, but its appearance is late.[87] Based on this, the hypothesis proposes that sexual experience does not prevent the development of pathologies in the prostate but delays their appearance. This proposal is supported by the fact that

the incidence of both death and new cases of prostate cancer continues to increase in a population that at least 90% has an active sexual life.[90] So, the obligatory question is, what are the molecular events involved in each condition? To date, there is no concrete answer, but progress has been made that indicates that sexual behavior promotes trophic changes in the MPG and in the prostate, which contribute to the delay in the onset of prostate diseases; however, to show this, more studies are still required in this regard.[87,90] What seems to be a fact is that the autonomic nervous system controls the function of the prostate and has an essential role in the initiation and/or progression of prostate diseases, but its control depends on the type of fibers that innervate the tissue. The parasympathetic system seems to have a stimulatory effect in promoting prostate cancer. It promotes the invasion effect due to the formation of newly formed parasympathetic cholinergic fibers and by activating type 1 muscarinic receptors, and it exerts a trophic effect by releasing NGF and GDNF.[84,103,104] For its part, the ß-adrenergic pathway increases the potential for metastasis by generating an inflammatory process induced by the infiltrate of macrophages and natural killer cells, inhibiting apoptosis, and generating a feedback mechanism between the stroma, cancer cells, and the nervous system.[105] Therefore, the nervous system is of therapeutic potential in order to control invasion and metastasis.[106] The idea to be considered should consider that invasion and metastasis depend not only on this system but also on the hormonal and the immune system, and the game between these three systems makes it very difficult to approach. Therefore, it is necessary to know the beginnings of cancer, which is still far from being known, but it could be an appropriate strategy in advanced cases.

7. Summary

This review analyzes the development and function of the prostate and the underlying hormonal regulation by testosterone and prolactin and the autonomic nervous system via the pelvic and hypogastric nerves, as well as the impact following the execution of sexual behavior that increases serum levels of testosterone and prolactin. In the prostate, sexual behavior increases cathepsin D, prolactin, and testosterone receptors, without affecting the receptors for acetylcholine and norepinephrine in the major pelvic ganglion, including trophic changes in both the ganglion and the prostate to promote fertilization. On the order hand, histological changes in the MPG and prostate, in animals with sexual experience, correlate with an increase of prolactin serum levels, short prolactin receptors in the prostate, androgen and muscarinic receptors in the MPG, and a decrease in testosterone serum levels and long prolactin receptors in the prostate. Although PRL seems a risk factor for generating diseases in the gland, it generally is not considered a treatment option, and even less the innervation of the prostate, notwithstanding that it is associated with prostate pathology. Now, we have the first steps to understand better the participation that each one plays in the evolution of the complicated diseases of the prostate.

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