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Review - Narrative

Expression of androgen receptors in the structures of vulvovaginal tissue

Santiago Palacios, MD

Abstract

Importance and Objective: Little is known about the role of androgens in the female genital tract, specifically in the vulvovaginal area. The abundance of androgen receptors in this area could help us to explain their role. The main objective of the present article is to review current data on androgen receptors in the different structures of vulvovaginal tissues.

Methods: A review of the literature using data from PubMed was carried out on androgen receptors in the vulva, labia majora and minora, vestibule, clitoris, and vagina. The effects of androgens and regulation of androgen receptors both in the embryo and in premenopausal and postmenopausal women were also reviewed. Given the characteristics of this review, we also analyzed animal studies and animal models of human disease. There were no filters or restrictions with respect to the date of publication.

Discussion: Androgen receptors have been detected throughout the genitourinary tract by means of Western blot, immunohistochemistry, ligand binding, and gene expression. They are present in the labia majora and minora, the clitoris, the vestibule, and in the three layers of the vaginal mucosa (epithelium, lamina propria, and muscularis). More specifically, studies on the labia majora have shown that androgen receptors seem to be particularly abundant in epidermal keratinocytes and in dermal fibroblasts. Androgen receptors are also abundant in the epidermis, especially in the keratinocytes, and in the dermis of the labia minora and vestibule, where they are more numerous than in the vagina. Androgen receptors have also been found in the Bartholin glands.

Conclusions: Estrogens play a major role in the maintenance of vaginal physiology. Although little is known about the role of androgens in the genital apparatus of women, specifically in the vulvovaginal area, the abundance of androgen receptors could enable us to explain their role. Androgens and estrogens play a major role in the maintenance of vaginal physiology. Better knowledge of the role of androgens and their receptors in vulvovaginal tissue would make it possible to discern their effects on female genitalia and help us to understand new therapeutic strategies.

Key Words: Androgen receptors – Clitoris – Labia majora – Labia minora – Vagina – Vestibule.

Hormones have an effect on the growth, development, differentiation, and sensitivity of the genitals. Studies on the action of hormones and their receptors suggest that female phenotypic differentiation of the external genitals is an active process that depends on both estrogens and androgens.[1,2] Furthermore, androgens and estrogens are essential physiological modulators in the maintenance of the structure and function of genital tissue.[3,4] The effects of estrogens on the genital apparatus are well known, as are the changes associated with their decrease during menopause.[5] Various studies have demonstrated the presence of estrogen receptors (ERs) on the vaginal walls, labia minora, vestibule, clitoris, and—albeit to a lesser extent—labia majora.[2,6]

In the labia majora, which are composed of skin, ERs have been found in luminal epithelial cells in the apocrine sweat glands and in dermal fibroblasts in the skin. They have, however, not been observed in the blood vessels of the skin or in the lymphatic system.[2] ERs are found in the epidermis and dermis of the labia minora,[2] as well as in the corpus cavernosum and smooth muscle of the clitoris, and are abundant in the three layers of the vaginal mucosa (epithelium, lamina propria [fibroblasts], and muscularis).[2] ERα is distributed in both the epithelium and in the stroma, with greater density in the parabasal cells. The cellular distribution of ERβ is similar to that of ERα, although ERβ are not as abundant or prominent.[7]

Women have a greater amount of androgens than estrogens both during reproductive life and in the postmenopausal

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From the Palacios Institute of Women's Health, Madrid, Spain.
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Address correspondence to: Santiago Palacios, MD, Palacios Institute of Women's Health, Antonio Acuña, 9, 28009 Madrid, Spain. E-mail: spalacios@institutopalacios.com

period.[8,9] Although little is known about the role of androgens in the genital apparatus of women, specifically in the vulvovaginal area,[10] the abundance of androgen receptors (ARs) could enable us to explain their role.[2,11] In fact, androgens contribute to the maintenance of the structure and function of genitourinary tissue. The effects of androgens may differ from those of estrogens or may complement the action of estrogens. The processes mediated by androgens may be involved in total or partial resolution of genitourinary syndrome in menopausal women.[10] Better knowledge of the role of androgens and ARs in vulvovaginal tissue would make it possible to discern their effects on the female genitalia and help us to understand new therapeutic strategies.

The main objective of the present article is to review current data on ARs in the different structures of vulvovaginal tissues.

METHODS

We carried out a review of the literature using data from PubMed on ARs in the vulva, labia majora and minora, vestibule, clitoris, and vagina. The effects of androgens and regulation of ARs both in the embryo and in premenopausal and postmenopausal women were also reviewed. Given the characteristics of this review, we also analyzed animal studies and animal models of human disease. There were no filters or restrictions with respect to the date of publication.

DISCUSSION

Androgen receptors

ARs, also known as NR3C4 (nuclear receptor subfamily 3, group C, member 4), are nuclear receptors that are activated via binding of androgenic hormones, including testosterone and dihydrotestosterone, in cytoplasm, before translocation to the nucleus.[12,13] ARs are encoded by the AR gene located at chromosome X in Xq11-12.[14]

The members of this receptor family are characterized by a single protein structure, which is composed of various functional domains: the hormone-binding domain, the DNA-binding domain, an amino-terminal domain involved in transactivation, the nuclear localization domain, and the dimerization domain.[15]

ARs comprise 918 amino acids and have an estimated molecular weight of 110 kDa.[16,17] The hormone-binding domain is located close to the carboxyl terminal region and is composed of a hydrophobic region, which in turn forms the hormone-binding site. The two predominant and natural androgens that bind to the AR are testosterone and 5α-dihydrotestosterone. In vivo and in vitro experiments have shown that 5α-dihydrotestosterone binds more avidly to ARs than testosterone and is more potent for inducing the biological response.[18]

The main mechanism of action of ARs is direct regulation of gene transcription. Binding of an androgen to an AR results in a conformational change in the receptor, which, in turn, leads to dissociation of heat shock proteins, transport from the cytoplasm to the nucleus, and dimerization. The dimer of the AR binds to a specific sequence of DNA known as the androgen response element. Several coregulators also play a role in transcription of ARs and influence their capacity to bind to ligands and DNA.[19] Upregulation or activation of transcription results in a more pronounced synthesis of messenger RNA, which, in turn, is translated by ribosomes to produce specific proteins. Insulin-like growth factor receptor 1 is a known target gene in the activation of ARs.[20] Therefore, changes in specific protein levels in cells constitute one way that ARs control cell behavior (Fig. 1).

ARs may be involved in actions that are independent of their interactions with DNA.[21] They interact with specific signal-transducing proteins in the cytoplasm. Binding of androgens to ARs in the cytoplasm can lead to rapid changes in cell function, irrespective of changes in gene transcription, such as changes in ion transport. This can in turn trigger release of intracellular Ca^{2+} and activate kinases such as MAPK, Akt, PKA, and PKC.[21,22]

Androgen signaling is linked to cell proliferation, differentiation, metabolism, and apoptosis, as well as to protein secretion in various tissues in both men and women.[10]

The decrease in androgen levels with age seems to correlate with a decrease in the quantity and expression of ARs.[23] Furthermore, administration of large doses of testosterone to women increases expression of mRNA in these receptors.[11] Both these observations have been demonstrated, since when androgen levels decreased after oophorectomy in rats, expression of ARs decreased. When testosterone was later administered, expression of ARs was restored in the vagina.[24] Furthermore, immunostaining studies also demonstrated a greater density of ARs in the vagina of ovariectomized rats supplemented with testosterone than in those that had not been administered a supplement.[25]

In addition to testosterone, 5α-dihydrotestosterone and estradiol regulate their own receptors, although each of these hormones could cross-regulate another receptor. Thus, administration of physiological levels of estradiol in ovariectomized rats slightly reduced immunostaining in AR in the vaginal epithelium and muscularis layer.[25] It, however, remains unclear whether or not testosterone regulates ERs.[10]

There is some debate about whether vaginal androgens interfere with the efficacy of aromatase inhibitors. Witherby et al[26] performed a study of postmenopausal breast cancer patients with vulvovaginal atrophy receiving aromatase inhibitors who were given testosterone in vaginal cream. After 4 weeks of treatment, both the symptoms and the signs of atrophy had clearly improved. These data could indicate the importance of local action via vulvovaginal ARs. ARs have been detected throughout the genitourinary tract by means of immunohistochemistry, Western blot, ligand binding, and gene expression. They have been observed in the labia majora and minora, the clitoris, the vestibule, and in the three layers of the vaginal mucosa (epithelium, lamina propria, and muscularis) (Table 1).[1,2,11,15,23,25,27]

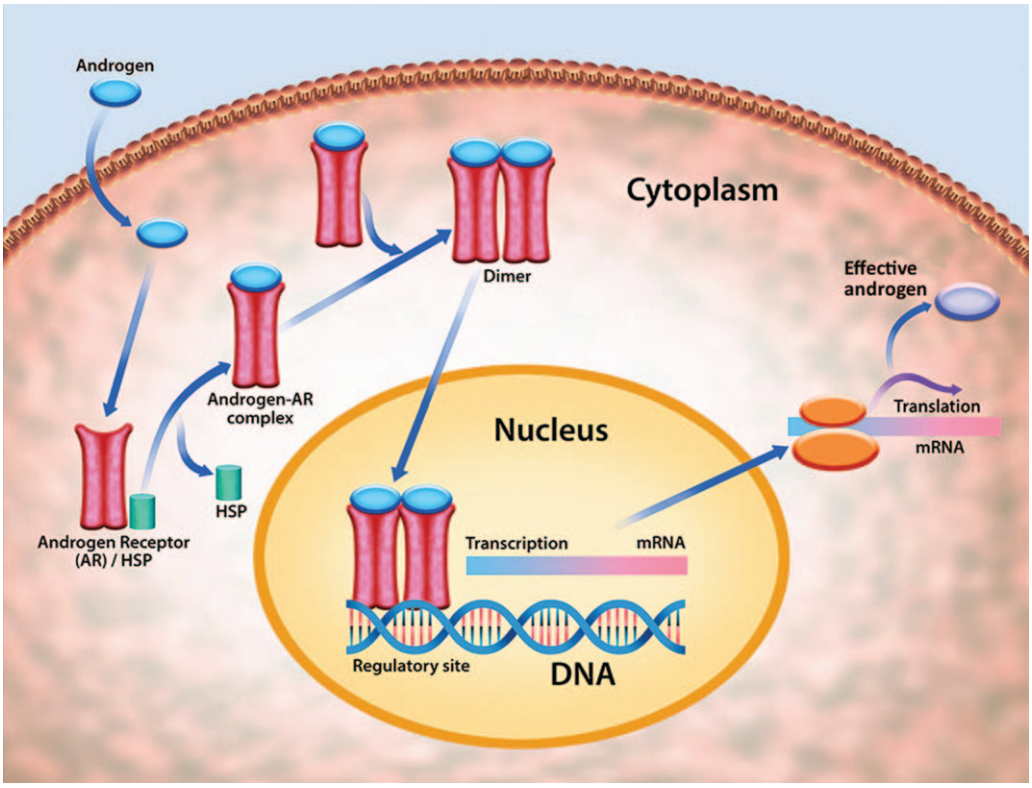

FIG. 1. Mechanism of action of androgen receptors.

Labia majora

The term ''labia majora'' is used to define the larger labia. The labia majora comprise a prominent pair of skin folds that form the lateral longitudinal borders of the pudendal cleft. The labia majora form the folds that cover the labia minora, the clitoris, the vestibule, the vestibular bulbs, the Bartholin glands, the Skene glands, the urethra, and the vaginal opening. The anterior part of the folds of the labia majora merges to form the anterior labial commissure directly below the pubic area. The posterior part of the labia majora merges to form the posterior labial commissure. The labia majora are approximately 7 to 8 cm long, 2 to 3 cm wide, and between 1 and 1.5 cm thick.[28]

After puberty, the external surface of the labia majora is covered with pigmented skin, which contains the sweat and sebaceous glands and is covered by hair. Each labium has an external pigmented surface covered with curly hair and an internal surface that is pink and smooth with large sebaceous glands. Between these surfaces, we find abundant lax connective tissue and adipose tissue mixed with smooth muscle that is similar to scrotal muscle, together with vessels, nerves, and glands.[29]

TABLE 1. *Androgen receptors located in the vulvovaginal area*

Labia majora	Epidermis (keratinocytes)
	Dermis (fibroblasts)
	Sebaceous glands (basal cells and sebocytes)
	Hair follicles (dermal papilla cells)
	Sweat glands (secretory cells)
Clitoris	
Labia minora and vestibule	Epidermis (keratinocytes)
	Dermis (fibroblasts)
Bartholin glands	
Vagina	Epithelium
	Lamina propria
	Muscularis
	Vascular endothelium

In females, in the absence of anti-Müllerian hormone, Müller's paramesonephric ducts form the fallopian tubes, the uterus, and the upper third of the vagina. The Wolff ducts degenerate owing to lack of androgen. The external genitals continue to develop until the sixth week, when we can see three projections around the cloaca, namely, the left and right cloacal folds and the genital tubercle. The cloaca, which is closed by the cloacal membrane, is divided into an anal part and a urogenital part. Toward the seventh week, these folds are known as anal and urethral folds. During the same week, the labioscrotal folds develop at the sides of the urethral folds, and the urogenital membrane ruptures to expose the cavity of the urogenital sinus to the amniotic fluid. The urogenital sinus remains as the vestibule of the vagina. The two urogenital folds of the genital tubercle form the labia minora and the labioscrotal folds swell to form the labia majora.[30]

The surface of the labia majora, as mentioned above, is covered with skin and is home to the characteristic hormonal receptors. For several years, studies have been performed to accurately locate the receptors of steroid hormones in human skin.[31] ARs are located mostly in keratinocytes in the

epidermis. In the dermis, they are detected in approximately 10% of fibroblasts. In the sebaceous glands, ARs are observed both in basal cells and in sebocytes. In the hair follicles, expression of ARs is limited to the dermal papilla cells. In the eccrine sweat glands, only a few secretory cells express ARs (Table 1).[31]

More specifically, studies on the labia majora have shown that ARs seem to be particularly abundant in epidermal keratinocytes and in dermal fibroblasts.[32,33]

Therefore, immunostaining is positive for ARs and ERs in the epidermis and dermis of the tissue of the labia majora.[2] Compared with human vaginal epithelium, immunostaining in the labia majora is more pronounced for ARs and less pronounced for ERs.[2]

Clitoris and vestibular bulbs

The clitoris is a sex organ that functions as a sensory organ. It can be divided into the glans and the body of the clitoris. The underlying tissue that forms the clitoris is the corpus cavernosum, which is a type of erectile tissue that merges together and extends toward the exterior of the vulva as the glans clitoris. The glans clitoris is the only visible part. Somatic innervation of the clitoris is via the dorsal nerve of the clitoris, a branch of the pudendal nerve, which is highly innervated and supplied by many blood vessels. It is estimated that the glans clitoris is innervated by approximately 8000 nerve endings. In fact, the glans clitoris has abundant cutaneous corpuscular receptors, that is, free nerve endings that provide information to the central nervous system.[34]

The body of the clitoris can reach 15 to 23 mm in total length, whereas the glans clitoris is 3 to 4 mm wide and between 4 and 5 mm long in its flaccid state. When erect, it can, however, reach up to 17 to 25 mm in length. The clitoris is the center of the orgasmic response and the embryological counterpart of the penis.[35]

At 3 months, the embryonic external genitals are differentiated after division into the urogenital sinus, which is part urinary and part genital. The genital area subsequently divides into the deep (or pelvic) area and the superficial area, which is in turn divided by the urogenital membrane and by the genital tubercle, from which the clitoris emerges.[30]

At this stage, ARs are already expressed, in much the same way as during the development of the penis at 8 to 9 weeks.[36] At 12.5 weeks, the human clitoris already expresses AR, ERα, and ERβ.[37]

The clitoris is sensitive to androgens during embryonic development. It, however, maintains its dependence on androgens in adulthood, because it continues expressing significant quantities of ARs, although most of the tissues in the developing female genital tract stop expressing ARs after the first trimester of pregnancy (Table 1).[38] In fact, in ovariectomized rats, treatment with testosterone was associated with increased vasodilation, which is critical for tumescence of the clitoris during sexual arousal.[39] This effect of testosterone was not due to the conversion to estradiol, because joint administration of testosterone and letrozole, an aromatase inhibitor, did not eliminate the response.[39]

The vestibular bulbs (counterpart of the bulb of the penis) are structures formed by the corpus spongiosum, which is a type of erectile tissue that is closely related to the clitoris. The vestibular bulbs arise near the inferior side of the body of the clitoris before extending toward the urethra and the vagina. In their flaccid state, they measure 3 to 4 cm in length.[40]

The vestibular bulbs are thought to work closely with the clitoris. During sexual arousal, the vestibular bulbs fill with blood. The resulting congestion exerts pressure on the corpus cavernosum of the clitoris and the glans of the clitoris. This pressure on the clitoris is thought to induce a pleasant sensation during sexual arousal. In hormonal terms, it behaves in parallel to the clitoris.

Labia minora

The labia minora are found inside the labia majora. They measure 3 to 4 cm and extend from the hood of the clitoris, forming a prepuce, to surround the urethral opening and the vagina, before finishing in what is known as the fourchette, which lies a few centimeters from the anus and thus forms the frenulum of the labia minora.[28,41] The tissue covering the labia minora differs from that of the labia majora. It is a richly irrigated and innervated mucous membrane and is therefore more sensitive. It is also more pinkish in color and does not have sweat glands or hair follicles.[27,40] The color, size, and appearance of the labia minora vary widely from woman to woman. In some cases, the labia are almost nonexistent, whereas in others they may be fleshy and protuberant. They are often asymmetrical.[42,43]

The labia minora contain erectile tissue composed of thick connective tissue that is rich in small blood vessels. During arousal, congestion of blood in the labia minora makes them rigid, and they double or triple in thickness. They are highly sensitive owing to the considerable number of sensory receptors and nerve endings. Genital corpuscles (typical receptors of the external genitals) and Krause-Finger corpuscles (highly sensitive tactile corpuscles) are abundant. Finally, we can also observe Pacinian and Meissner corpuscles (sensory cutaneous mechanoreceptors).[43-45]

As in the case of the clitoris, the labia minora and vestibule are formed from the genital part of the division of the urogenital sinus at 3 months. The urogenital sinus persists as the vestibule of the vagina. The two urogenital folds of the genital tubercle form the labia minora.[30]

ARs are abundant in the epidermis, especially in the keratinocytes, and in the dermis of the labia minora and vestibule, where they are more numerous than in the vagina. This observation is true for both premenopausal and menopausal women (Table 1).[2,46]

Vestibule

In human anatomy, the vaginal vestibule (vestibule of the vagina, vulvar vestibule) refers to that part of the vulva located between the labia minora. The limit between the

vagina and the vaginal vestibule is defined by the opening of the urethra. At this point, we also find the hymen. The vestibule is surrounded by glands that ensure vaginal moistness (since there are no glands in the vagina itself). These include the Bartholin glands (greater vestibular glands), the paraurethral glands (''female prostate''), and the lesser vestibular glands.[43] The secretion from these glands, which is released during orgasm (female fluid emission) toward the vaginal vestibulum via the urethral meatus or via the openings of the paraurethral ducts, contains prostate-specific antigen and would be the equivalent in the male of the release of seminal liquid by the prostatic urethra.[47]

In addition to the smooth muscle in the wall of the vestibule, we find a striated sphincter, which closes the vaginal vestibule. The lateral vestibular walls also contain a special erectile tissue (bulb), as mentioned above. The border between the vestibule and the labia minora is known as Hart's line, which demarcates the change from the vestibule to the labia minora.[43]

The number of ARs found in the vestibule is high and similar to that found in the labia minora.[2,46] ARs have also been found in the Bartholin glands (Table 1).[48]

Vagina

The vagina is an elastic muscular canal measuring 7 to 10 cm in length that extends from the vulva to the cervix, where it finishes in the anterior fornix and posterior fornix. The vaginal canal is located between the urethra and the bladder in the anterior direction and the rectum in the posterior direction. The opening of the vagina is in the posterior part of the vestibule. A thin perforate layer of hymen partially covers the external vaginal opening. The vaginal canal has an external fibrous adventitia, a medial layer of smooth muscle, and an internal mucous membrane. The internal mucous membrane has two transversal folds that are clearly visible; these serve to increase the surface area for extension and stretching.[49,50]

The walls of the vagina are composed of stratified squamous cells that do not contain keratin.[51] These layers are divided into basal cells, parabasal cells, superficial squamous (flattened) cells, and intermediate cells. The basal layer of the epithelium is the most active in terms of mitosis and produces new cells. The superficial cells are continually detaching and are replaced by the basal cells,[49,51] with up to 40 cell layers in place.[52] The lamina propria is rich in collagen fibers, fibroblasts, blood vessels, and lymphatic vessels. The internal muscle layer is composed of smooth muscle fibers. The vagina does not contain glands. Because the vaginal epithelium, however, contains low levels of lipids, it enables[2,53] fluids to pass through the vaginal wall.[54] The cells of the vagina respond to estrogens and androgens. Receptors for these hormones are found in the three layers of the mucous membrane,[2,11] which in turn produce a response that is crucial for the maintenance of the vaginal walls.[54]

The vaginal plate is the precursor to the vagina.[52] During development, the vaginal plate begins to grow where the fused ends of the paramesonephric ducts (ie, the Müllerian ducts) enter the posterior wall of the urogenital sinus as the sinus tubercle. As the plate grows, it considerably separates the cervix and the urogenital sinus. Eventually, the central cells of the plate break down to form the vaginal lumen.[52] This generally occurs between weeks 20 and 24 of development. Opinions on the embryological origin of the vagina are contradictory. Most follow the description by Koff (1933), which postulates that the upper two-thirds of the vagina originate in the caudal part of the Müllerian ducts, whereas the inferior part develops from the urogenital sinus.[51-53] Therefore, the vagina is formed by a tissue with two different embryological origins.[51-53]

Estrogens regulate the proliferation and differentiation of cells in the epithelium of the vaginal mucosa. This is seen in the abundance of ERs in the basal and suprabasal vaginal epithelium.[2,55] The abundance of ERs in the cells of the vaginal stroma in the lamina propria also suggests that interactions with the stromal epithelium could be involved in the regulation of estrogen in the vaginal epithelium during adulthood. AR protein, however, has been detected throughout the human vagina (mucosa, submucosa, stroma, smooth muscle, and vascular endothelium).[2,11] Similar positive immunoreactivity findings have been reported for ARs in the epithelium, lamina propria, blood vessels, and muscularis layer of the monkey vagina (Table 1).[56] Furthermore, the enzymes involved in androgen biosynthesis (17β-hydroxysteroid dehydrogenase and 5α-reductase) are expressed at high levels in the stratified squamous epithelium of the monkey vagina and at lower levels in the muscularis layer and in the walls of the blood vessels.[21,56] These data lead us to believe that both estrogens and androgens play a major role in the maintenance of vaginal physiology.

CONCLUSION

Our data indicate that ARs can play an important role in the vulvovaginal area. Although the number of ERs seems to be greater in the vagina, the number of ARs is greater in the vestibule, labia minora, and labia majora.[2,11,32,33,38,46,56]

The role of estrogens at vulvovaginal level is well known, with increased superficial cells, reduced basal cells, decreased pH, and improvement in the main symptoms, such as dryness and dyspareunia.[57] Little is known about the role of androgens at the vulvovaginal level. The large amount of ARs in the vestibule and labia majora and minora lead us to consider a possible role of androgens in local immunity and inflammatory processes. Thus, the biological function of epidermal ARs in the labia majora may be necessary for specialized differential functions of the keratinocytes. In addition to their structural function, epidermal keratinocytes play a key role in the immune and inflammatory response of the skin.[58,59] Furthermore, the high number of ARs in the clitoris points to a possible role in increasing the sensitivity of the clitoris and in sexual functioning.[34,36,38] In women who received long-term treatment with testosterone (intramuscular Testoviron depot 100 mg every 7-10 days for ≥1 year) before

surgery, expression of the mRNA of ARs was significantly greater in the vaginal tissue than in postmenopausal women.[11] Similarly, ovariectomy in rats downregulated expression of ARs, and testosterone replacement restored AR expression in the vagina.[24] Immunohistochemistry also demonstrated greater density of ARs in the muscle layer of the vagina of ovariectomized rats who received testosterone supplementation.[25] Therefore, circulating testosterone is positively correlated with expression of ARs in the vagina.

In order to understand the role of androgens in the vulva and vagina, it is, however, necessary to take into account other concepts, such as upregulation/downregulation of ARs at this level. In addition, receptor subtypes with different signaling pathways and polymorphisms in the receptor that can alter interactions with other macromolecules increase the complexity of the responses.[10] Circulating testosterone is positively associated with expression of ARs in the vagina. It is unknown whether a critical concentration of testosterone is necessary to maintain appropriate levels of ARs.[11,24,25] Although local estrogens play a more important role in vulvovaginal atrophy than systemic estrogens,[60] we do not know whether or not this is the case with androgens.

It is important to highlight the potential presence of polymorphisms in both ERs and ARs. These could affect susceptibility to certain clinically significant conditions as hormone levels decrease. Women who develop vestibulodynia are more likely to harbor longer CAG repetitions in the AR gene; this genetic characteristic is associated with a reduced capacity of response to androgens in the target tissue.[61,62] More than 1,000 mutations have been described in ARs, and most are involved in persons affected by androgen insensitivity syndrome, that is, individuals with the XY karyotype but a female appearance. In any case, we know very little about polymorphisms in ARs in women or their clinical consequences.[63]

Demonstration of the presence of ARs in the various areas of the vulva and vagina indicates that androgens are likely necessary for maintaining the physiology and morphology of tissue in the vagina, vestibule, clitoris, and labia minora and majora. This concept should be further investigated to establish the precise role of androgens in this context.

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