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Exploration of Ion Channels in the Clitoris: a Review

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Abstract

Purpose of the Review This review investigates known research on ion channels expressed in the clitoris. Specifically, discussing the role these channels play in clitoral arousal, their contributions to sexual dysfunction, and their potential use as a pharmacological targeted treatment. In addition, we propose channels that should be considered as candidate proteins involved in female sexual dysfunction.

Recent Findings Review of studies published from 1811–2017, found that only BK_{Ca}, SK, and TRPA1 channels have been explored in the clitoris. These studies have identified these channels in clitoral tissue and have suggested their involvement in the nitric oxide-cGMP mediated pathway of erection. However, these studies have not resulted in additional or improved treatment options for female patients with sexual dysfunction. Finally, we suggested the consideration of voltage-gated sodium channels as candidate proteins to explore in sexual dysfunction, due to the comorbid relationship with epilepsy.

Summary Based on these findings, further research is needed into these channels and their role in female sexual arousal. Investments into this area of research have the potential for improving our understanding of sexual dysfunction of arousal, improving pharmacological treatments, and ultimately improving quality of life for patients.

Keywords Clitoris · Ion channels · Sexual dysfunction · Arousal

Introduction

The clitoris is a major structure involved in sexual behavior. Coupled with the vagina, it plays an important role in the experience of sexual stimulation, progressing to arousal, and ultimately, orgasm. Under normal conditions, this experience is achieved with visual and sensory stimulation leading to an increase in clitoral/genital blood flow, the relaxation of smooth muscles, and the increase in vaginal size, allowing for penetration [1–4]. However, for an estimated 20–22% of the general population, this important aspect of life is altered resulting in sexual dysfunction (SD) [5]. SD occurs when there are disturbances in the ability to experience sexual pleasure and/or respond to sexual stimulation. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) defined three categories for SD in females: female orgasmic disorders (FOD), genito-pelvic pain/penetration disorders (GPPPD), and female sexual interest/arousal disorders (FSIAD) [6]. Patients with FOD experience abnormalities in orgasms, including delays, infrequencies, and/or their complete absence. In contrast, GPPPD is defined as pain or discomfort during or while attempting intercourse, resulting in reduced desire. Lastly, individuals affected with FSIAD experience lack or significantly reduced sexual interest/arousal, persisting for a minimum of 6 months. This includes reduced or absent sexual genital (including the clitoris) sensation or arousal during sexual activity. Due to remaining taboos around female sexuality and limited available treatment options, many patients go undiagnosed and untreated.

To date, limited information is available on the physiological mechanisms and biochemical responses that underlie normal female sexual arousal response and the involvement of the clitoris. This dearth of knowledge led us to investigate the areas in which research on the clitoris has focused. We utilized the database Pubmed and found 2021 articles on the clitoris, dating from 1811–2017. We then categorized them into one of

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the following topics: anatomical anomaly, anatomy/physiology, cancer/tumor, chromosomes, diseases/disorders, development, evolution, genital mutilation, hormones, intersex, protein expression/ ion channels, reproduction, sexual arousal, sexual behavior, sex differentiation, sexual dysfunction, sexually transmitted infections (STIs), surgery, theory, transgender, or vagina/vulva. A miscellaneous category was also included that accounted for papers that did not fit into one of the categories. Descriptions of each category can be found in Table 1. From this investigation, we found that the majority of research conducted on the clitoris during this period had focused on two topics: Disease/Disorders (16%) and Surgery (14%) Table 2. These two categories focus on conditions that affect the anatomical features of the clitoris and any surgery done to reconstruct or repair damage. In comparison, fewer papers focused on normal anatomy/physiology (9.4%) and sexual arousal/stimulation/ sensation/orgasm (7.5%). It is also important to note that of the 2021 papers examined, 1665 (82.4%) were based on human subjects, whereas only 365 (17.6%) focused on animal models. Of the models investigated, the most common were rodents (i.e., mice and rats). These are valuable models for studying clitoral tissues, as there are anatomical similarities with the human structure [7]. In mice, the clitoral bulbs are formed form erectile tissue that surrounds the urethra. Similar to the human clitoris, the corpora cavernosa of the mouse clitoris is homologous to that of the mouse penis. In addition, smooth muscle tissue in mouse corpora cavernosa vasculature, suggests its role in arousal. Clitoral stimulation and the effects of behavior has been evaluated in rat model systems. Frequent clitoral stimulations were able increase proceptive sexual behaviors in female [8], activate brain areas associated with reward [9], and induced sexually conditioned partner preference [10]. Taken together, this suggests that the rodent clitoris has anatomical and behavioral similarities to the human clitoris and that the model should be further utilized in studying SD and exploring potential drug treatments. Overall, our review of the literature suggests that past research has focused primarily on surgical improvements and has lacked in utilizing animal models for better understanding of normal physiology in regards to sexual arousal.

Of particular interest were papers that examined the expression of ion channels in the clitoris. We found that only 25 (1.5%) published articles on the clitoris focused on these essential physiological elements. This low number highlights a deficit in research regarding these cellular components. We were surprised considering the role that ion channels play in regulating the flow of ions in and out of cells, neuronal excitability, and their use as common pharmacological targets. Disease-causing mutations in the genes that encode ion channels are known as "channelopathies" and can be found in a wide variety of disorders including epilepsy [11], migraines [12], blindness [13–15], deafness [16, 17], diabetes [18], hypertension [19], asthma [20], cardiac arrhythmia [21], irritable bowel syndrome [22], and cancer [23]. In addition, many individuals with these conditions report some form of SD, either due to comorbidity factors or the side effects of the targeted medications for these conditions [24–31]. Taken together, these findings warrant further exploration of ion channels as potential gene targets for studying normal clitoral physiology and could enable better treatments for women with SD. In this review, we will discuss the literature on current knowledge of ion channels in the clitoris and propose potential ion channels as candidate pharmacological targets for SD.

BK_{Ca} Channels

Of the papers examined, the large conducting, calcium-activated potassium channels (BK_{Ca}) were identified as a major protein involved in the erection of smooth muscle tissues [32•]. It is of particular interest due to its role in the molecular mechanism of penile erections via the nitric oxide (NO) pathway. In short, NO is released from nonadrenergic-noncholinergic nerves during sexual stimulation, relaxing smooth cavernous muscle tissues and increasing blood flow to the penis, promoting tumescence [33–35]. During this process, smooth muscle relaxation is believed to results in part from NOs activation of the second messenger cyclic guanosine monophosphate (cGMP). Consequently, its accumulation triggers the activation of cGMP-dependent kinases and subsequently, their phosphorylation of BK_{Ca} channels. Once activated, these channels are responsible for the hyperpolarization of arterial and cavernosal smooth muscle tissues in the penis, resulting in closure of voltage-gated Ca^{2+} channels [36–38], which ultimately reduces Ca^{2+} influx, causing the tissues to relax allowing blood flow. This process can be terminated by the hydrolysis action of phosphodiesterase 5 (PDE-5) on cGMP, thereby allowing muscles contractions to resume [39].

Prior to 2002, many assumed that the mechanisms underlying clitoral erections were similar to penial erections, due to their structural homologies during embryonic development [40]. There had also been indirect evidence of structural similarity when sildenafil was found to be an effective PDE-5 inhibitor in human clitoral corpus cavernosum tissue [41]. However, there had been no direct evidence to support this idea. Parks et al., was the first to identify that a NO-cGMP pathway was involved in the regulation of clitoral tumescence in rabbits [42]. It was further elucidated by Gragasin et al. with ex vivo and in vivo methods in rat clitoris that the cGMP-dependent mechanism, involved the activation of BK_{Ca} channels, leading to clitoral smooth muscle relaxation [32]. This was a major finding, as it identified a pathway that could be used to study the physiology of female SD.

Pharmacological agents that activate BK_{Ca} channels could serve as potential treatments for SD that involve dysfunctions in clitoral erections. Under normal physiological conditions,

Table 1 Descriptions of criteria used to categories articles in the clitoris literature

Category	Description
Anatomical anomaly	Focuses on the clitoris under abnormal circumstances (ex: enlarged clitoris)
Anatomy/physiology	Focuses on the clitoris under normal circumstance
Cancer/tumor	Focuses on tumors and forms of cancers that spread to and/or affect the clitoris
Chromosomes	Focuses on chromosomal analysis
Disease/disorder	Focuses on any specific disease or disorder that directly affected the clitoris. Cancer/tumors are excluded from this category
Development	Focuses on the anatomical and physiology development of the clitoris during embryogenesis
Evolution	Focuses on the differences and conservation of the clitoris between species
Female genital mutilation (FGM)	Focuses on circumcisions and removal of the clitoris
Hormones	Focuses on the receptors of hormones expressed on the clitoris and their biochemical responses
Intersex	Focuses on variation in the clitoris as it pertains to intersex individuals
Protein expression/ion channels	Focuses on research involving these proteins and their anatomical expression or physiological effects
Reproduction	Focuses on procreation, including pregnancy and contraceptive topics as it relates to the clitoris
Sex differentiation	Focuses on describing normal sex characteristics (i.e., anatomy, hormones, chromosomes)
Sexual arousal/stimulation/sensation/orgasm	Focuses on research dealing with sexual pleasure, sensation, stimulation, and the physiology underlying these mechanisms
Sexual behavior	Focuses on the clitoris as it relates to sexual behavior
Sexual dysfunction	Focuses on difficulties with achieving and/or maintaining an orgasm, sexual arousal, and/or libido. This includes pelvic floor disorders and priapism.
Sexually transmitted infections (STIs)	Focused on STIs that specifically affect the clitoris
Surgery	Focuses on surgeries that are specific to the clitoris. This includes functional, reconstructive, and cosmetic.
Theory	Analysis of the thoughts and widely held beliefs surround the clitoris.
Transgender	Analysis of the clitoris after transitioning from birth sex
Vagina/vulva	Focuses on issues pertaining to the vagina and/or vulva that indirectly include the clitoris
Miscellaneous	Includes studies that do not failing into any of the defined categories

drugs that open or activate this membrane-bound protein would cause the efflux of K^+ with an increase of intracellular Ca^{2+}. This would result in hyperpolarization of the cell membrane causing the subsequent decrease in cell excitability and the relaxation of smooth muscle tissues leading to an erection. Pharmacological studies investigating the efficacy of BK_{Ca} channels as a potential drug target have been limited. The BK_{Ca} channel activators NS1619 [36], NS11021 [43], NS-8 [44], LDD175 [45], and iberiotoxin [37] have each demonstrated the ability to open/activate BK_{Ca} channels and enhance erectile response in human and rat penile tissues to varying extents. For example, in combination with the PED-5 inhibitor tadalafil, NS-8 enhanced vasodilation and erectile function in male diabetic rats [44]. Despite these results, there has not been progression in moving these potential agents towards clinical trials or investigating their efficacy in clitoral tissues. This is of importance because of the limited improvements in sexual impairments seen in women taking the commonly prescribed PDE-5 inhibitors such as Sildenafil [46], suggesting the need for additional treatment options.

To better understand the role of BK_{Ca} channels in the process of clitoral erections, some questions remain. Of importance is the expression profile of the channel in the clitoris over age. Studies have suggested that poor sexual function in women was correlated with age [47–50]. This could be due in part to the reduction of estrogen seen with increased age [51]. However, a better understanding of the age-related expression profile of BK_{Ca} channels in clitoral tissue is important, as it could provide insights into its role in SD. Additionally, the role of clitoral erections in the complex nature of female sexual arousal is not clear. When women are sexual stimulated, the dorsal clitoris and cavernosa clitoral arteries increase in blood flow and fill the corpus cavernosa. Similar to the process in males, the increase in blood supply leads to an increased clitoris size and tumescence [1, 3, 52]. Together these events stimulate pelvic floor muscle contractions, which ultimately lead to an orgasm. In rat models of sexual behavior, it was identified that clitoral relaxation and engorgement results from NO-mediated relaxation of smooth muscle cells by a mechanism involving cGMP-dependent activation of BK_{Ca} channels [32•]. Therefore, failure to achieve adequate tumescence may be an important factor in SD in women. Despite this relationship, it is unclear from available data how frequent dysfunctions in clitoral erections occur.

Table 2. Categorical analysis of articles on the clitoris from 1811-2017

Category	Total (out of 2021)	Percentage (%)
Anatomical anomaly	62	3.1
Anatomy/physiology	190	9.4
Cancer/tumor	125	6.2
Chromosomes	7	0.35
Disease/disorder	322	16
Development	31	1.5
Evolution	4	0.20
Genital mutilation	148	7.3
Hormones	59	2.9
Intersex	193	9.5
Miscellaneous	84	4.2
Protein expression/ion channel	25	1.2
Reproduction	43	2.1
Sex differentiation	36	1.8
Sexual arousal/stimulation/sensation/orgasm	151	7.5
Sexual behavior	27	1.3
Sexual dysfunction	61	3.0
STIs	12	0.59
Surgery	275	14
Theory	3	0.15
Transgender	21	1.0
Vagina/vulva	142	7.0

SK Channels

Similar to BK_{Ca} channels, the potassium SK channels are responsible for hyperpolarizations and are activated by increases in intracellular Ca^{2+}, leading to relaxation of smooth muscle tissues. Unlike the large conductance currents seen in BK_{Ca} channels, SK channel activation results in small potassium conductances and are responsible for regulating medium lasting after hyperpolarization (i.e., refractory periods) during action potentials [53]. Therefore, they are important regulators of neuronal excitability. Structurally, the transmembrane protein consists of 6 domains [54], with an c-terminus bound to the Ca^{2+} sensor calmodulin [55].

Of particular interest is the SK channel, SK3 (gene name *KCNN3*). SK3 has been found in high levels in human corpus cavernosum of the clitoris compared with the penis and was suggested as a potential drug target for erectile dysfunction [56••]. In addition, a 5-fold increase in SK3 was seen in penis samples of males that were on chronic estrogen treatment for sex change procedures. Estradiol was also shown to reduce tension in colonic smooth muscle tissue that had an increased expression of SK3 [57]. This suggests that estrogen may play a role in regulating the expression of this channel. We speculate that the low levels of estrogen seen during menopause could impact SK3 expression, leading to altered clitoral erections in women during these periods.

In addition to its expression in human clitoral tissues, SK3 is also expressed in neurons of the locus coeruleus [58], hypothalamus [59], basal ganglia [60], and the limbic system [61, 62], suggesting that alterations in this channel could impact cognitive behavior and emotionality. The commonly prescribed antidepressant fluoxetine (Prozac), a selective serotonin reuptake inhibitor, has been shown to block the activity of SK channels, preventing small conductance currents in HEK cells [63]. In addition, fluoxetine has been demonstrated to impair libido in women [64, 65]. Considering many patients with affective disorders, especially those taking SSRIs also experience SD, it may be of interest to determine if SSRIs exacerbate these symptoms through SK3 channel disruptions and develop alternative methods to relieve these side effects. It is also possible that due to the wide expression pattern of these channels in the CNS and PNS, altered function may impact multiple system. Nevertheless, future research should include investigating the relationship between SK channels and serotonin in sexual arousal.

The development of drugs that target SK channels, with the goal of improving hyperexcitability have not resulted in clinical treatments. For example, apamin (Octodecapeptide apamin), a bee venom, has been one of the most explored compounds in the field [57, 63, 66]. It has been demonstrated to block SK channels, preventing its activation in HEK cells [67]. However, its efficiency varied among the classes of SK

channels and is commonly used to determine the efficacy of potential modulators (NS8593, NS11757) [66]. Future studies should evaluate the efficacy of these potential modulators in cells systems and animals models of sexual behavior.

TRPA1 Receptors

More recently, the transient receptor potential cationic channel ankyrin 1 (TRPA1) expressed in sensory neurons has been identified in human clitoris [68••] and the human vagina [69]. This channels structure consists of six domain transmembrane protein, with a transmembrane loop connecting S5 and S6 [70]. It was originally described as a noxious cold sensor [71, 72]; however, it is now believed to be a non-selective mechno- and pain sensor channel that is sensitive to multiple exogenous and endogenous compounds. Well known activators include arachidonic acid, isothiocyanates (the active ingredient in mustard and wasabi), dihydrogen sulfide, cinnamaldehyde (cinnamon extract), and allicin (garlic extract) [73–75]. Furthermore, one of the main functions of the channel is to conduct Ca^{2+} in response to sensory stimuli [76]. Although TRPA1 is poorly selective for Ca^{2+}, its contribution adds to overall changes in intracellular levels [77]. Therefore, TRPA1 dysfunction could lead to alterations in smooth muscle contraction and relaxation.

Studies investigating this channel in human clitoral tissue and the vagina [68, 69], found TRPA1 in neurons expressing NO, suggesting a functional role in the cGMP pathway. However, the biological function of the channel in human sexual tissues is not known. We speculate that when activated via mechanical or chemical modulators, the additional intracellular Ca^{2+} via the TRPA1 channels adds to the net Ca^{2+} generated by the NO-cGMP pathway, ultimately leading to changes in the smooth muscle tissue. Therefore, TRPA1 may function in sexual tissue by modulating the effects of the NO-cGMP pathway. It is also important to note that it is not clear what the function of its endogenous modulations on sexual arousal. Taken together, these results suggest a complex role for this channel in these tissues and the need for additional studies.

No studies to date have investigated sexual behavior in TRPA1-null mice. These animals demonstrated diminished aversion to mustard oil, reduced pain response, and reduced sensitivity to extreme cold temperature (0°C) [72], providing support for the channel's role in modulation via isothiocyanates, and pain and temperature sensing. In addition, they appear to breed efficiently and lack no other apparent behavioral alteration. However, the quality of their copulation, as measured through proceptive and receptive sexual behaviors, is unknown. Alterations in these behaviors would provide insights into the protein's potential role in SD and as a therapeutic drug target due to its proposed NO-cGMP modulatory effects.

Voltage-Gated Sodium Channels

Examination of the literature revealed that the role of voltage-gated sodium channels (VGSC) in the clitoris, and female sexual arousal was not known. VGSC are a major class of proteins found in the plasma membranes of excitable tissues, comprised of a pore forming α subunit and auxiliary β subunits [1–4, 78–80]. These channels allow for the influx of Na^+ upon changes in the membrane potential. Therefore, playing a major role in the initiation and propagation of action potentials and overall neuronal excitability. There have been 10 VGSC subtypes identified in mammals to date: $Na_v1.1$–$Na_v1.9$, and Na_vX [79–82]. Of the 10, only $Na_v1.4$ is not expressed in the nervous system. Altered VGSC function has been identified in various conditions including epilepsy ($Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.5$, and $Na_v1.6$) [83–86], pain ($Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$) [87–89], migraines ($Na_v1.1$) [90–93], autism ($Na_v1.1$ and $Na_v1.7$) [94–98], and multiple sclerosis ($Na_v1.5$) [99]. Many individuals with these conditions report some form of SD, either due to comorbidity factors or the side effects of the conditions targeted medications [100–102].

Of particular interest is the voltage-gated-ion channel proteins implicated in epilepsy. Epilepsy is associated with an increased risk of SD [103]. It has been reported that between 14 and 50% of women patients with epilepsy have complaints of issues with sex [104], ranging from decreased libido to less frequent orgasms compared with women in the general population [105]. In addition, clinical data has demonstrated that epilepsy may alter aspects of reproduction including loss of ovarian cycle, irregular cycle duration, and anovulatory cycle [106, 107]. Experimentally, chronic seizures have been shown to reduced measures of sexual motivation and performance in rat models of pilocarpine, suggesting the SDs seen in patients with epilepsy maybe independent of the effects of anti-seizure medications [108, 109]. The SDs can be further complicated by the consumption of these medications, due to mechanisms that potentially alter reproductive hormone levels [110, 111]. However, from the clinical literature, it is not clear if the women in these studies had mutations in VGCS. The sexual behavior or health is also not discussed in the clinical literature of patients with forms of epilepsy from VGSC mutations. This is of interest considering approximately 40% of epilepsy conditions are believed to be genetic in nature, including those that encode ion channels [45]. Clarity on the form of epilepsy affecting these patients may provide insights into the mechanisms and proteins involved in or associated with SDs, leading to new options for pharmacological treatment.

Conclusions

In conclusion, we have identified a disparity in our understanding of ion channels expressed in the clitoris and their role

in sexual behaviors. Much of the previous research in the clitoris investigated diseases and disorders that impacted the structure and/or surgical methods for improvement. This was important work, as it has helped in our understandings of the complexity of the human structure. However, very little work has been done to investigate the expression and function of critical proteins such as ion channels in the clitoris. This is important as 61 (3%) of the papers we investigated made a connection between altered clitoral structure and/or function and SD. Considering the importance of ion channels in maintaining cell excitability, alterations in their functions could lead to issues with sexual arousal.

To date, our most extensive knowledge of ion channels in the clitoris is based on the NO-cGMP-mediated mechanism of smooth muscle relaxation in the penis. In that, BK_{Ca} and SK3 channels are involved. Both are expressed in the clitoris, and their potential use as pharmacological targets has been suggested. However, much more research is needed to answer questions regarding their expression patterns in the clitoris, function in clitoral arousal and the potential for side effects due to actions in the central nervous system. TRPA1 channels have been newly identified in sexual tissue and have potential as pharmacological targets based on their proposed modulatory function. Lastly, we proposed VGSC as potential drug targets due to the comorbid relationship in patients with epilepsy and SD. Further investigation is needed through the use of epilepsy rodent models with known ion channel mutants. In conclusion, we have demonstrated that more research in this critical area is needed in order to better our understanding of the sexual arousal and the involvement of the clitoris.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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