Endothelin I Activates the NAADP Signaling Complex on Myometrial Smooth Muscle Cell

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This is the first study of endothelin I effects on mobilization of lysosomal calcium stores in uterine smooth muscle, secondary to NAADP-dependent pathway activation. Endothelin I is able to initiate the NAADP signaling system, which is responsible for about 28.43% of whole intracellular calcium dynamics during myometrial induced contraction.

Abstract

There are two main types of intracellular calcium stores: smooth endoplasmic and lysosomal, the last one being activated by nicotinic acid adenine dinucleotid phosphate (NAADP). ***Objective.*** *We decided to study the role of NAADP-sensitive calcium stores on endothelin I (E I)-induced uterine contraction, using bafilomycin B1 (BAF), a lysosomal vesicles destroyer. This is the first study on E I effects on mobilization of lysosomal calcium stores în uterine smooth muscle, secondary to NAADP-dependent pathway activation.* ***Study Design.*** *We compared the E I 10-8M-induced contractions on non pregnant rat uterine strips, before and after BAF 10-6M administration.* ***Results.*** *BAF decreased the amplitude of E I-induced contractions with 28,43±11% and the frequency with 7,3±3%. No impact on automatic uterine activity was noted.Conclusions. The calcium mobilized from NAADP-sensitive stores has important roles on the amplitude of E I-induced contraction. Its functions on membranal depolarizing (phenomenon responsible for frequency of contractile oscillations) is far less intense, either on induced or on spontaneous contractions.*

Keywords: *myometrium, calcium stores, lysosomes, NAADP, endothelin I, bafilomycin B1*

Introduction

Two main types of internal calcium stores are actually well pharmacologically characterized: smooth endoplasmic reticular and lysosomal. Other sites (mitochondrial, caveolar etc) remain with an unclear physiological role.

Lysosomes are able to store a significant quantity of calcium that can be mobilized by nicotinic acid adenine dinucleotid phosphate (NAADP)[1].

This compound appears after the stimulation of membranal G protein coupled receptors by almost all ocytocics[2], including endothelin I (E I), but the exact pathway of appearance of this second messenger (NAADP) is still unclear.

In order to investigate this pathway, we designed the first study on endothelin I effects on mobilization of lysosomal calcium stores in uterine smooth muscle, secondary to NAADP-dependent pathway activation.

Study Design

We used non-pregnant Sprague-Dawley female rats, weighting 180-200 g. Only animals in diestrum were selected, by vaginal smear examination.

The animals were kept in cages, with 8 hours of light/day, with permanent water supply and with a normal diet, established by the Nutrition and Epidemiology Departments.

They were killed by rapid decapitation, after being put to sleep with thiopental sodic 1g/kg. The trunks were sectioned and the two uterine horns from each animal were introduced in Krebs solution, with the following composition (mM): 127 NaCl, 1.9 KCl, 1.2 KH_2PO_4, 2.4 $CaCl_2$, 1.3 $MgCl_2$, 26 $NaHCO_3$ and 5 glucose, oxygenated with a mixture of 95% O_2 and 5% CO_2 and thermostated at 37°C.

For each uterine horn 2 strips of 3 mm length were cut.

All experiments were performed under the American University Laboratory Animal Care Committee Agreement.

The uterine strips were mounted vertically in a 5-ml organ bath and connected to a force transducer (ML T0201/RAD; ADInstruments, Colorado Springs, CO, USA) coupled to a Quad Bridge Amplifier (ADInstruments). Contractions were recorded using a PowerLab system and Chart 5 software (ADInstruments).

After 15 minutes of equilibration, the strips were washed with warm Krebs solution and, after 10 minutes, a control contraction to E I 10-8M, was induced. The contraction was quantified during 10 minutes.

The strips were washed 4 times, each time 15 minutes and after each washing bafilomycin B1 (BAF) was added, up to a 10-6M-concentration in the organ bath. We waited for 5 minutes after the last BAF administration and E I was readministered in the organ bath, in the same concentration. The last contraction obtained was compared to control.

For more accurate evaluation of the effects of BAF on myometrial E1-induced contraction, the action of BAF

alone on muscular strips was also registered, in orcder to showi the direct effects (if any) of BAF on spontaneous uterine activity, using the same protocol.

Eight determinations were performed for each type of experiment.

The contractile response was analyzed by using 2 parameters:

a) area under the contractility curve.

b) frequency of myometrial contractions.

Statistical analysis

Two-way ANOVA was used; a P-value of <0.05 was considered statistically significant.

Chemicals and reagents

Experiments were performed with endothelin I (Sigma-Aldrich) and bafilomycin B1 (Sigma-Aldrich).

Results

Spontaneous activity of 3mm uterine slices was characterized by a mean area under the contractility curve (contractions amplitude) of 104.37±39g.s. and by a frequency of oscillations of 14±6/10min.

Administration of endothelin I 10-8M strongly increased the uterine fragments contractility, to274,4±83g.s and the frequency to 16±7/10min.

BAF decreased the area under the contractility curve with 28,43±11% and the frequency of the myometrial contractions with 7,3±3% ($p < 0.05$) (Figures 1, 2).

During administration of BAF alone, a weak and inconstant decrease of the spontaneous uterine activity was registered: 0-5% (Figure 3).

Disscusion

BAF blocks vesicular H+-ATP-ase [3], inducing lysosomal alkalinisation. If the exposure is longer (more than 30 minutes), the alkalinisation is so intense that lysosomal destruction occurs. Secondary to this phenomenon, the calcium contained in these organelles (lysosomal calcium) disappears[4].

Comparing the data before and after BAF administration, it can be quantified the role of lysosomal calcium stores on E I-induced myometrial contraction: 28.43±11%, with a stronger impact on amplitude and a much weaker effect on frequency - 7.3±3% (Figure 2).

It is probable that the weak decrease of spontaneous uterine activity after BAF administration alone is more the result of the normal slight reduction of the autonomic contractions, after more than one hour of strips activity, than a direct effect of BAF on myometrium (Figure 1).

This means that lysosomal calcium stores have almost no role on spontaneous membranal depolarising.

Conclusions

As we previously said, NAADP can mobilize calcium from lysosomes after the stimulation of membranal G protein coupled receptors by E I.

We can conclude that the activation of the NAADP-dependent signaling system by E I is implicated mainly on force generation during uterine contraction. ■

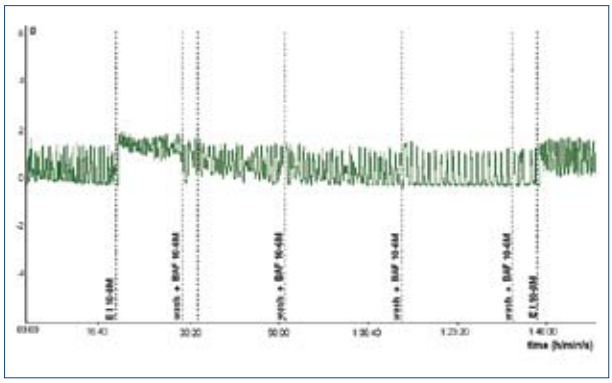

Figure 1. Effect of BAF 10-6M on E I 10-8M induced myometrial contraction

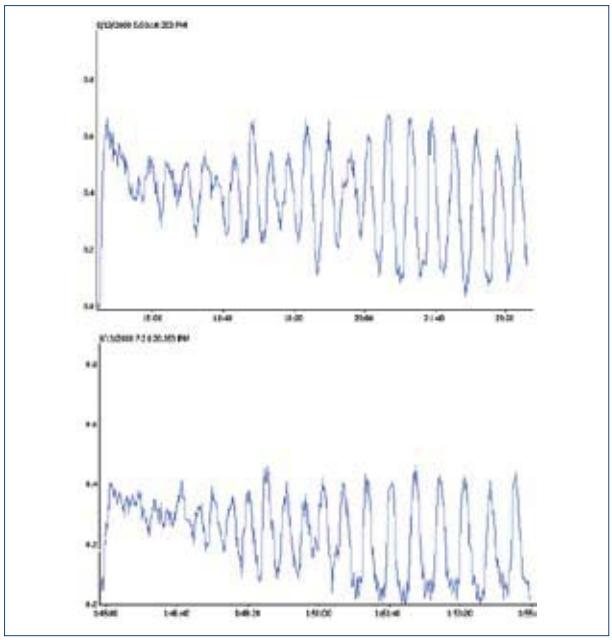

Figure 2. Details of the E I 10-8M-induced contraction before (on the top) and after BAF 10-6M administration (on the bottom)

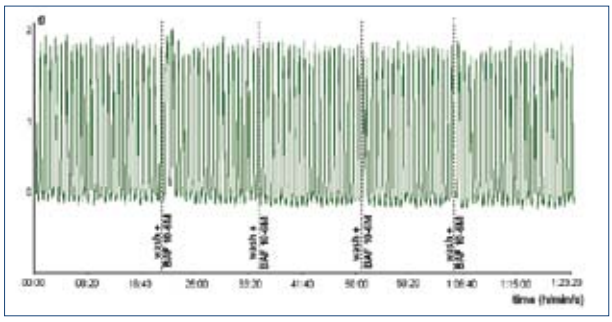

Figure 3. Effect of BAF 10-6M on spontaneous myometrial activity

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New Approach on Hypoactive Sexual Desire Disorder

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Abstract

Dysfunction of female sexual desire, arousal, or orgasm affects approximately 30% of women. Early attempts to treat female sexual dysfunction arose out of programs developed for male erectile dysfunction and have proven largely unsuccessful. A new wave of targets is now being pursued; many of these targets are postulated to modulate central pathways. Classical neurotransmitter systems, such as dopamine and serotonin are receiving the most attention. Early clinical data look promising; however, clinical trial methodology in female sexual dysfunction is not well developed and only further testing will determine whether these treatments satisfy patient need.

Keywords: *female sexual dysfunction, hypoactive sexual desire disorder, flibanserin*

One of the first innovations of the XXI century was the concept that sexuality has not an age restriction. There is a tendency in developed countries for prolonged life expectancy with better quality of life, which conveys a good maintenance of capacities such as physical, psychological, and sexual. This progress facilitates the recognition by WHO in 1992 of sexual dysfunction as a pathology that can affect man and woman.

Female sexual dysfunction (FSD) is characterized by a disturbance in sexual desire and/or in the psycho-physiological changes that make up the sexual response. The disturbance must cause marked distress or interpersonal difficulty and must not be better accounted for by the effects of another (non-sexual) psychiatric disorder, medical disorder, or substance[1].

FSD is a prevalent, yet largely unrecognized, disorder. Approximately 30-50% of women report sexual dysfunction and would seek treatment is a smaller proportion[2]. FSD has historically been considered a primarily psychological disorder, though it is now clear that it can also occur secondarily to other organic medical problems. This is a clear distinction from male erectile disorder, which is usually thought of as organic in origin. The classification of FSD is largely derived from models of normal female sexual function. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classifies the subtypes of FSD into hypo-active sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), and orgasm disorder. The two other subtypes are sexual aversion disorder and sexual pain (Table 1)[3].

HSDD is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association, as diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and lack of responsive desire that causes marked distress or interpersonal difficulties and is not caused by a medical condition or drug[4]. HSDD is a medical condition that remains largely under-diagnosed[5].

Hypoactive Sexual Desire Disorder (HSDD) is a complex affliction which can have many causes - in many women the cause will never be determined. Often the causes of HSDD will depend on the type of HSDD. Typically men are only classified as one of three subtypes, while women can sometimes relate to one or more of the different types of HSDD.

The 3 Subtypes of HSDD are:

1. Lifelong or Generalized HSDD - The patient has little or no desire for sexual stimulation (either with a partner or alone) and never has.

2. Acquired/Situational HSDD - The patient was previously sexually interested in present partner, but now lacks sexual interest in them - but still has desire for sexual stimulation (ie. alone or with someone other than present partner).

3. Acquired/Generalized HSDD - The patient previously had sexual interest in present partner, but now lacks interest in sexual activity - either partnered or solitary.

Obviously, lifestyle factors also influence the desire for sex. A single working mom who is overwhelmed by family needs may feel too exhausted to relax, kick back and fantasize about sex - let alone engage in it! However, sometimes a medical condition is the underlying cause of low libido, including:

Table 1 Definitions of FSD from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders[3]

Hypoactive Sexual Desire Disorder (HSDD)	Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity
Female Sexual Aversion Disorder	Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner
Female Sexual Arousal Disorder (FSAD)	Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement
Female Orgasmic Disorder (FOD)	Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase
Dyspareunia	Recurrent or persistent genital pain associated with sexual intercourse
Vaginismus	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse

■ **Medication Use:** Many commonly prescribed drugs, such as antihypertensives, antidepressants and birth control pills, interfere with sex drive, arousal and orgasm by affecting the balance of sexual hormones and the transmission of chemical messengers. For instance, antidepressants known as selective serotonin reuptake inhibitors combat depression by increasing the production of serotonin in the brain. Unfortunately, serotonin dampens sexual desire[5].

■ **Menopause:** The onset of menopause, either surgical or natural, is characterized by a gradual decline of the hormones estrogen, progesterone and testosterone. Reduced testosterone levels, in particular, can lead to a "sudden or gradual" decline in libido. Ironically, the conventional hormone replacement regimen of estrogen and progesterone given to relieve menopausal symptoms can make matters worse, because estrogen increases a protein (called steroid hormone-binding globulin) in the blood that binds to testosterone, causing it to become less available to the body.

■ **Depression:** A common symptom of depression is diminished sex drive, which, in turn, can exacerbate depression. Studies indicate that 12 percent of all women will experience clinical depression at some point in their lives. As mentioned, one of the side effects of the popular antidepressants Prozac, Paxil and Zoloft is loss of libido. Dysthymia is a lower-grade form of depression that is not easily diagnosed because you can function with it. A woman with dysthymia may feel isolated and overwhelmed and withdraw from sex and social activities[5].

The algorithm developed by Basson is a useful tool to establish a diagnosis (Figure 1)[6].

Before to start any treatment it is important to emphasize that impairment in sexual activity or frequency only becomes a dysfunction when distresses the patient. Non-pharmacologic and pharmacologic therapies are available to treat sexual dysfunction in women and both should be considered in a basic approach. Non-pharmacologic therapy includes providing information and education about normal anatomy, sexual function or normal changes of aging, lifestyle changes such as well-balanced diet, smoking cessation and exercise, strength improvement of the pelvic floor muscles, enhance tactile stimulation and eliminate routine. Pharmacologic therapy may include sexual steroids, sildenafil, dopaminergic drugs, prostaglandins, melanocyte-stimulating hormone, adrenoceptor antagonists, herbal therapies and other substances in development[7]. This large patient population currently has few effective treatment options and the enormous success of Sildenafil (Viagra) and similar drugs for erectile dysfunction suggests there is willingness to seek treatment for sexual disorders.

A. Non-pharmacologic therapies:

Counseling - Psychological and relationship issues often underlie, exacerbate, or are amplified by, sexual dysfunction in one or both partners. As an example, a major cause of decreased sexual desire and response is a relationship with limited communication or underlying conflict.

Sex and couples therapy - Women with sexual dysfunction will often benefit from referral to a sex and/or couples therapist. Couple's counseling is effective when there is relationship conflict or limited communication. Sex therapists often are highly trained counselors, with special expertise in human sexuality. They may be physicians, psychologists or social workers with additional training and experience.

Sex therapists educate women and men about the normal sexual response cycle and effectively deal with cultural or religious concerns regarding sexuality. Therapists assign specific exercises, which aid many women and couples with sexual dysfunction. In one study, 65 percent of 365 couples undergoing sex therapy for a range of sexual dysfunctions described their treatment as successful.

Examples of sex therapy exercise include instruction in the appropriate use of vaginal dilators, which is highly effective in treating most cases of vaginismus and dyspareunia. Another approach is sensate focus exercises to help couples increase mutual sexual pleasure, minimizing the importance of orgasm as the principal goal of sexual encounters[2].

Sex therapists work to improve communication between couples and often help negotiate a mutually accep-

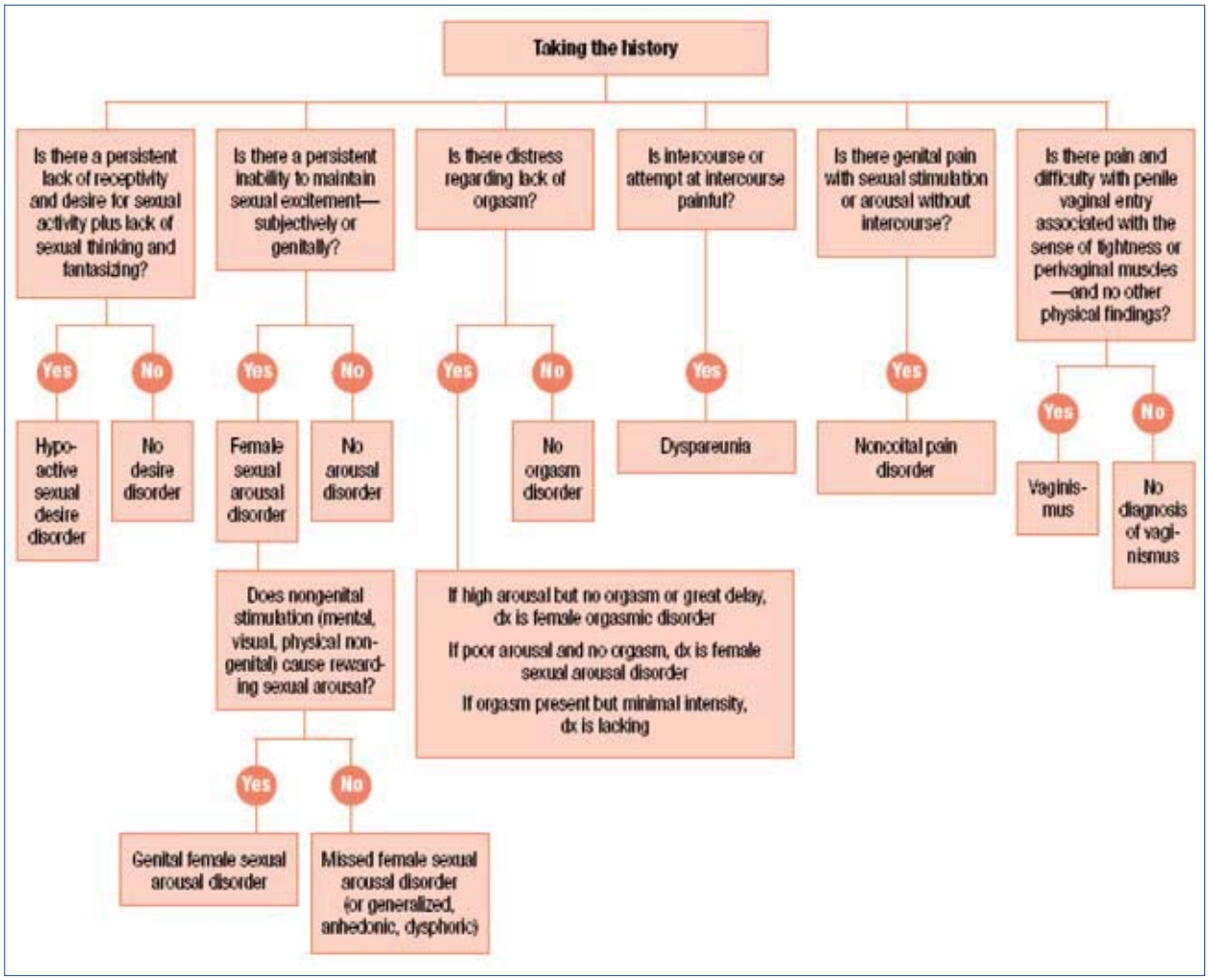

Figure 1. Establishing a diagnosis of sexual dysfunction - Basson Algorithm[6]

table frequency of sexual activity when varying levels of sexual interest are present and causing discord. They may direct patients to a wide range of helpful resources, including book lists, visual aids and devices.

Given the efficacy and high degree of safety of sex therapy, consultation with a sex therapist generally should be considered a prerequisite to a trial of pharmacologic therapy for most women with sexual dysfunction.

Psychodynamic therapy - Although relationship counselors and sex therapists are very helpful for psychologically healthy individuals, women with psychiatric disease will benefit from appropriate referral. Psychiatric disease, especially depression and anxiety, is associated with an increased likelihood of sexual dysfunction. Treatment of the underlying psychiatric problem, with appropriate pharmacology and/or psychodynamic therapy can lead to an improved sexual life. Prior physical, emotional or sexual abuse or substance abuse disorders also affect sexual function and may be addressed effectively in this setting.

As pharmacologic treatment of psychiatric illness is associated with sexual dysfunction, the expertise of a psychopharmacologist may be required when sexual problems precede, or are exacerbated by psychiatric medications.

Lifestyle changes - Fatigue, stress and lack of privacy contribute significantly to low libido and sexual problems for women. Often reducing stress with support groups, yoga or other relaxation techniques or exercise, or assistance with childcare responsibilities and housework results in improved sexual interest and satisfaction. Encouraging couples to establish a regular "date night" and to spend an occasional night or two away from family responsibilities can lead to significant improvements in sexual interest[2].

Research on sexual function consistently demonstrates increased libido and pleasure in new relationships. Although women should not be advised to improve their sex lives simply by seeking out new partners, they should be encouraged to bring novelty to their current relationships. Reading books about sexuality, visiting a store with items designed to increase sexual pleasure and expanding the typical sexual repertoire effectively increase libido and response[7].

Improving body image - A woman's view of her own body affects her sexual interest and satisfaction. Overweight women with sexual dysfunction should be assisted with weight loss. In addition, many women note improvements in their sex lives when they initiate a regular exercise program.

Lubricants - Lubricants during intercourse and nonhormonal vaginal moisturizers can be useful for both pre- and postmenopausal women with vaginal dryness and dyspareunia.

B. Peripherally acting agents

PDE5 inhibitors

Following the enormous success of PDE5 inhibitors (sildenafil-Viagra®, vardenafil - Levitra® and tadalafil - Cialis®) for the treatment of male erectile disorder, it was not surprising that attention turned to FSD to see whether they would be similarly successful in women. In common with the penis, the clitoris is derived from the same embryonic stem cells and possesses corpus cavernosal tissue[8]. During female arousal, the vagina also becomes engorged. PDE5 is present in human clitorial and vaginal tissue[9] and has been shown to relax human vaginal smooth muscle strips[10] and increase blood flow into dog vagina and clitoris[11].

Early clinical trials carried out in women with HSDD and FSAD demonstrated subjective improvements in arousal and orgasm as assessed by questionnaires[12]. However, subsequent studies in mixed FSD populations did not show any benefit of sildenafil[13]. Although sildenafil has a hemodynamic effect on female genital arousal, this does not seem to translate reliably into a positive subjective effect on arousalnor desire and, so, is not viewed by many women as a successful treatment for mixed FSD.

Neutral endopeptidase inhibitors

Vasoactive intestinal peptide (VIP) is one of the major vasoactive neurotransmitters found in the vasculature of the vagina. It is a potent vasodilator that is postulated to have a role in the control of vaginal blood flow[14]. VIP is a 28 amino acid peptide, which is unsuitable as an oral therapy for FSD. Neutral endopeptidase is a principal degrading enzyme of VIP, which is also present in vaginal and clitoral tissues. Potent selective and orally bioavailable inhibitors of NEP have been sought as potential treatments for FSD. The hypothesis under test is that inhibition of NEP will increase circulating levels of VIP and thereby facilitate increases in vaginal and clitoral blood flow in the presence of sexual stimulation.

To date, no clinical data have been reported on the efficacy of these peripherally acting agents on FSD or indeed their effect on vaginal or clitoral blood flow.

Topical PGE1 agonists

PGE1 has a wide range of actions, including inhibition of platelet aggregation, inhibition of gastric secretions, and relaxation of smooth muscle. The PGE1 receptor responsible for smooth muscle relaxation is the EP2 receptor that is found on the vaginal, uterine, and penile smooth muscle cells among many other tissues. Alprostadil is a synthetic analogue of PGE1. Alprostadil was initially developed as a treatment for erectile disorder. In females, two topical formulations of alprostadil are in phase III trials for FSD. Alprostadil is applied in a gel/cream/liquid formulation to the vulva and clitoris with the aim of producing vasodilation and thus vaginal lubrication and the warm/tingling sensation reported by women as a part of sexual arousal. So far, alprostadil significantly increased the number of satisfactory sexual encounters above that seen with placebo. The response does not appear to be dose dependent. The most common side effects of alprostadil are local edema and vaginal burning, itching, and soreness, which appear to be dose related. These side effects are reported as mild to moderate and easily tolerated. Large, long-term Phase III trials are still required to better determine efficacy and safety before this treatment can reach the market for FSD.

C. Centrally acting agents

The failure of the peripherally acting agents suggested that centrally acting agents may be more appropriate for the treatment of FSD.

Psychotropic agents

A possible benefit from dopamine agonists was suggested by sexual effects reported in women with Parkinson's disease treated with these agents.

Apomorphine is a dopamine agonist used off-label for the treatment of male erectile dysfunction. A two-week randomized cross-over trial of 50 premenopausal women reported treatment with apomorphine improved orgasm, sexual enjoyment and satisfaction[15]. Notably, only 47 percent of subjects completed the study, possibly due to side effects, which include nausea, vomiting, dizziness, and hypotension.

Bupropion

One randomized trial of 75 premenopausal women with HSDD and without underlying depression reported increased sexual pleasure, arousal and orgasm with bupropion - used for the treatment of major depressive disorder, including seasonal affective disorder (SAD); adjunct in smoking cessation, (sustained release 300 mg/d) compared with placebo[16].

Data from uncontrolled trials suggest that bupropion treatment of patients with SSRI-associated sexual dysfunction is beneficial.

Flibanserin

A pharmacologic treatment for hypoactive sexual desire disorder (HSDD) is under investigation and is also being reviewed by the Food and Drug Administration, but is not yet commercially available[16]. Flibanserin, which was initially studied as a possible antidepressant, has central effects on serotonin, dopamine and norepinephrine. Preliminary data from several large, multicenter randomized trials in premenopausal women with HSDD noted improvement in sexual desire (flibanserin versus placebo: 21 versus 10 percent of women reported desire was much or very much improved) and satisfying sexual events (0.7 per month).

Flibanserin displays antidepressant-like activity in most animal models sensitive to antidepressants. Such activity, however, seems qualitatively different from that exerted by other antidepressants. Flibanserin seems to act via direct or indirect stimulation of 5-HT(1A), DA, and opioid

receptors in those animal models. Flibanserin does not display consistent effects in animal models of anxiety and seems to exert potential antipsychotic effects. Flibanserin may induce some sedation but does not induce observable toxic effects at pharmacologically relevant doses.

D. Herbal supplements

Many women are interested in trying over-the-counter herbal supplements, which are advertised widely and claim to increase sexual desire and pleasure. Women should be informed that the safety and efficacy of these products are unproven, there is minimal regulatory oversight, and they are often costly. Nonetheless, given a 30 percent predicted placebo response and few reported side effects, women may elect a trial of these alternatives.

E. Hormonal modulators

The sex hormones have long been known to modulate sexual function. Receptors for these hormones are widely distributed in both central and peripheral tissues.

Tibolone

Tibolone is a synthetic steroid whose metabolites have estrogenic, progestagenic, and androgenic properties.

In randomized trials, tibolone appears more effective than estrogen/progestin therapy for treatment of sexual dysfunction in postmenopausal women[17]. However, the beneficial effects of either of these treatments on sexuality are modest and may not outweigh the risks.

Testosterone

Older studies of women who undergo surgical menopause reported that 30-50% of patients experience a decrease in sexual desire, though more recent reports have not demonstrated this decline[18]. Oophorectomy results in a decrease in circulating androgen levels because the ovaries produce approximately 50% of the testosterone in women. Several early studies have suggested that libido can be maintained if these women are treated with a combination of testosterone and estrogen. Given the above, pharmaceutical companies have tried to produce a testosterone based replacement therapy to treat HSDD. Improvement in desire, arousal and orgasm were all observed, but the increase in frequency of satisfying sexual events did not quite reach statistical significance.

An additional limitation of testosterone therapies is their potential adverse effects, particularly following long-term usage. Hirsutism, acne, and masculinization are the most obvious side effects of testosterone therapies, coronary heart disease, stroke, and venous tromboembolic disease were all increased.

Follow-up - After initiating therapy for sexual dysfunction, patients should be seen for regular follow-up visits, approximately every three months, until effective interventions are identified and the sexual problem has improved. Patients may then be seen every 6 to 12 months, depending on the potential risks of the treatments selected. Patients using pharmacologic therapies will need to be monitored for drug-related risks and side effects at these visits. Treatment efficacy is best assessed by patient self-report of improvement of symptoms.

Over the past five years, great progress have been made in both in recognition of female sexual dysfunction as a genuine medical disorder and in treatments to address it. The early attempts to transfer treatments for male erectile disorder to the female population have been largely unsuccessful, probably because in many women it is deficit in subjective desire and arousal that cause the problem, not physiological arousal of the genitals. The available data suggests that current treatments may be safe and efficacious; however, further clinical trials are required before their full efficacy and safety are well described. The majority of FSD patients are currently poorly treated and so the arrival of these novel treatments in the market place is eagerly awaited. ■

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