Melanocortins in the Treatment of Male and Female Sexual Dysfunction

Annette M. Shadiack*, Shubh D. Sharma, Dennis C. Earle, Carl Spana and Trevor J. Hallam

Palatin Technologies, Inc., Cranbury, NJ

Abstract: Melanocortinergic agents are currently being investigated for a possible therapeutic role in male and female sexual dysfunction. These investigations were sparked by findings that systemic administration of a synthetic analog of alpha-MSH, MT-II, causes penile erections in a variety of species, including humans. Several other melanocortinergic agents including HP-228, THIQ, and bremelanotide (PT-141) have since been shown to have erectogenic properties thought to be due to binding to melanocortin receptors in the central nervous system, particularly the hypothalamus. Bremelanotide, a nasally administered synthetic peptide, is the only melanocortinergic agent that has been clinically studied in both males and females. Data from Phase II clinical trials of bremelanotide support the use of melanocortin-based therapy for erectile dysfunction. Studies using animal models have demonstrated that pre-copulatory behaviors in female rats analogous to sexual arousal are evoked, and preliminary clinical data also suggest a role in promoting sexual desire and arousal in women. Based on bremelanotide clinical experience, administration of a melanocortin agonist is well tolerated and not associated the hypotension observed with phosphodiesterase-5 inhibitors currently used to treat erectile dysfunction. This review discusses investigations of melanocortin agonists for the treatment of sexual dysfunction with emphasis on proposed sites and mechanisms of action in the central nervous system that appear to be involved in melanocortinergic modulation of sexual function. Current research validates use of melanocortinergic agents for the treatment of both male and female sexual dysfunction.

Keywords: Melanocortin agonist, intranasal, sexual dysfunction, sexual arousal, erectile dysfunction, female sexual arousal disorder, bremelanotide, PT-141.

BACKGROUND AND INTRODUCTION

Disorders of sexual function are highly prevalent in men and women worldwide and have now gained acceptance as a general public health issue affecting quality of life. This review focuses specifically on current and emerging treatment options for both male erectile dysfunction (ED) and female sexual arousal disorder (FSAD). Sexual dysfunction, and ED in particular, is associated with an enormous burden of illness [1-2] and poor quality of life [3-4].

ED is defined as the persistent inability to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse [5]. ED can be related to vasculogenic, neurogenic, pharmacologic, or psychogenic factors, or mixed causes.

The prevalence and incidence measures of ED vary due to numerous factors including methodological differences between studies, age groups included in the studies and by the definition of the specific condition under study [5-7]. In the United States, the prevalence of erectile dysfunction is believed to be 5% of males at age 40 and 15-25% of males at age 65 [5]. It is estimated that between 7 and 20 million men suffer from ED. However, estimates can go as high as 30 million if men with partial erectile dysfunction are also included in the estimate [5]. The study of incidence of ED in a mostly white, randomly selected population of men in the Massachusetts Male-Aging Study estimated that the annual risk of ED is 26 cases per 1000 men [8]. In general, the annual incidence rate increases with age, but the age-adjusted risk also correlates with the presence of hypertension, diabetes, heart disease and lower education [8]. Depression as well as some medications are also associated with a higher probability of ED [9]. In addition, the prevalence and severity of ED increase with age [8-11].

Although prevalence, incidence and risk have been studied to some degree, there is a conspicuous dearth of epidemiological data on ED [6] and an overwhelming need for further research on mechanism, prevention, treatment and impact of ED [5], as well as a need for longitudinal studies [7].

*Address correspondence to this author at Palatin Technologies, Inc., 4C Cedarbrook Drive, Cranbury, NJ 08512; Tel: (609) 495-2207; Fax: (609) 495-2202; E-mail: ashadiack@palatin.com

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A relatively small proportion of men with ED (10-30%) seek treatment [4, 6], there may be under-reporting of ED in physician records [6] and a likely reluctance of patients and physicians to discuss ED [5]. Both patient and physician lack of awareness about treatment options may contribute to the under-treatment of ED [5].

FSAD and other disorders of female sexual function are not fully understood and have recently been redefined to help clarify the characteristics and factors involved. The American Urological Association Foundation has clarified that arousal disorder has 2 components; subjective arousal and genital arousal [12]. S*ubjective Arousal Disorder* is characterized by absent or reduced feelings of arousal (excitement or pleasure) from any type of stimulation. In contrast, *Genital Arousal Disorder* is characterized by absent or impaired genital arousal (swelling of the vulva or vaginal lubrication) from any type of sexual stimulation and reduced sexual sensations [12]. Subjective and genital arousal disorders can occur independently or in combination. Moreover, subjective arousal is not necessarily a good measure or correlate of genital response or arousal [12]. Subjective arousal is affected by a variety of medical, biological, psychological factors. The prevalence of FSAD is unknown in part because there are currently no protocol or specific objective measures that can be used to establish a diagnosis of FSAD [12], and there are no FDA-approved drug treatments for the disorder.

A high percentage of men and women with sexual dysfunction have a partner who also has sexual dysfunction. Among women whose male partner has ED, 60% had low sexual interest and 44% had insufficient lubrication [13]. Preclinical and clinical data suggest that melanocortin (MC) agonists may act centrally to impact sexual arousal in males and subjective arousal and desire in females. A single MC agent, therefore, offers an exciting and novel approach for the treatment of both male and female sexual dysfunction.

CURRENT THERAPEUTIC STRATEGIES FOR ED AND FSAD

ED

Strategies for treating ED include phosphodiesterase 5 (PDE-5) inhibitors, dopamine receptor-2 agonist (apomorphine) and synthetic prostaglandin E_1 (alprostadil).

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Alprostadil promotes erections by acting as a vasodilator, relaxing the corpora cavernosal smooth muscle, and thereby increasing blood flow to the penis**.** It can be administered via fine needle injection into the shaft of the penis, or urethral suppository. These routes of administration are associated with side effects that include pain and penile fibrosis [14-15]. Although considered to be a safe and effective treatment for ED, the route of administration may not be acceptable or tolerable for some patients. Although the suppository administration may be more tolerable, it is not as efficacious in the treatment of ED as the intracavernosal injection [15].

Topical alprostadil cream is under investigation for its use in erectile dysfunction. Data thus far suggest it has a small but statistically significant effect on improving erectile function. Mild to moderate adverse events include pain, burning and erythema in the genital application area [16].

PDE-5 inhibitors (sildenafil, tadalafil and vardenafil) augment smooth muscle relaxation and vasodilation and facilitate penile erection in the presence of sexual stimulation via accumulation of cyclic guanosine monophosphate (Fig. **2**). Each of the three PDE-5 inhibitors currently on the market possess different pharmacokinetic properties and duration of action [17], but they all interact with nitrates and are therefore contraindicated for a subpopulation of patients with ED who require nitrate-based vasodilators. Although considered first-line therapy, PDE-5 treatment failure is common [18], and may be associated with reduced response to drug as well as vascular and neurogenic disorders [19].

Sublingual administration of apomorphine acts centrally on dopamine-2 receptors to promote penile erections. It was approved in Europe (but not by the FDA in the US) for the treatment of ED and was subsequently withdrawn from the market for commercial reasons. It is effective in a small proportion of men with ED [20], and it is not considered as effective as sildenafil [21], particularly for men with arteriogenic ED [22]. It may be best suited for men with mild ED [18]. The main side effects are headache and nausea [20].

FSAD

Current strategies for treating FSAD include treatment with androgens such as a testosterone patch, topically applied alprostadil or PDE-5 inhibitors; however, none of these strategies have been FDA-approved for treating FSAD. Historically, women with sexual interest or desire disorder have been given testosterone or other androgen treatments off-label. Low androgen levels in women are associated with aging and menopause, some medications, and following surgical removal of the ovaries. Although there are a lack of population-based studies to demonstrate the link between sexual function and androgen levels in women [23], a systematic review of studies of post-menopausal women who have appropriate estrogen levels shows that testosterone (in low-dose regimens) may improve multiple aspects of sexual function, including desire [24]. Testosterone can be administered in a variety of ways including orally, via intramuscular injection and transdermal patches. Common side effects include acne and hirsuitism as well as possible effects on liver function and lipid profiles [23-25]. These effects are dependent on both dose and route of administration [23]. However, the main concern and the purported reason for the lack of FDA approval for the testosterone patch for the treatment of hypoactive sexual disorder in women is the lack of long-term safety data on use of testosterone and its relation to breast cancer, stroke and myocardial infarction [23-25]. Moreover, since testosterone can be aromatized to estrogen, there may be additional risks associated with testosterone as a treatment for sexual dysfunction [23]. Long-term safety and efficacy data on androgens in female sexual dysfunction are lacking.

The clinical utility of topical application of alprostadil cream as a treatment for FSAD is currently under investigation. As a topical vasodilator, it does increase clitoral and labial engorgement in healthy women, as measured by duplex ultrasound [26]. The most common side effect is mild or moderate local burning and itching in the genital region where the cream is applied [27-28]. However, efficacy reports from clinical trials of alprostadil in treating FSAD have been mixed. Although some studies have reported improvement on specific measures of arousal, the results have not been consistent among studies [27-28].

Clinical trials and off-label use of oral PDE-5 inhibitors for women with sexual dysfunction are based on the premise that the vascular component of the physiology of female sexual arousal (clitoral engorgement) via increased accumulation of cyclic GMP is similar to that of penile erection in males [29-30]. However, the role of this mechanism in vaginal vasocongestion as an arousal response remains unclear. Reviews of published studies reveal that there is no conclusive or consistent benefit of sildenafil for women with sexual dysfunction (although some women may show significant improvement on some measures) [31-34].

MELANOCORTINS AND SEXUAL FUNCTION

A variety of neuropeptide hormones have been shown to cause penile erection following intracerebroventricular (ICV) administration in rodent models. This includes alpha melanocyte stimulating hormone (alpha-MSH) and adrenocorticotropic hormone (ACTH) [35], both post-translational modifications of pro-opiomelanocortin (POMC) sharing a common N-terminal 13-amino acid sequence. Discovery of spontaneous penile erection behavior caused in human subjects by systemic subcutaneous administration of a synthetic analog of alpha-MSH, known as melanotan-II (MT-II), has opened up this new area of research establishing the role of melanocortin receptor (MCR) agonists for the treatment of sexual dysfunction. MT-II (Fig. **1-A**) is a cyclic lactam bridged heptapeptide that constrains an optimized His-Phe-Arg-Trp tetrapeptide segment of α-MSH and ACTH. MT-II was shown to cause penile erection in 8 out of ten human subjects having either psychological (16) or organic (17) erectile dysfunction. However, side effects of MT-II administration included facial flushing, stretching-yawning syndrome, nausea, and vomiting [36-37]. Based on these adverse effects and the small therapeutic window, investigators doubted the clinical utility of MT-II [37]

Since the description of the erectogenic properties of MT-II, efforts to identify other such agents focused both on peptides and small molecules. Bremelanotide (PT-141; Fig. **1B**) developed by Palatin Technologies, Inc., is a peptide that is currently being evaluated in confirmatory phase-II studies for treatment of both male and female sexual dysfunctions. Bremelanotide is delivered intranasally using a disposable single use metered dose delivery device.

The structure-function relationship investigations for developing MC-4R agonists for treatment of sexual dysfunction have been largely dependent on successful testing of the agent in animal models. Differential ability of molecules to cross the blood-brain-barrier complicates developing a SAR for this CNS target. Therefore, *in vivo* studies often require cumbersome ICV administration of melanocortinergic agents. However, a number of selective agonists have also been tested for their efficacy in producing penile erection in a rat model after IP or IV administration. Once an agent is identified for its potential in causing penile erection, its specificity of action can be determined by additional administration of MCR subtype-specific competitive antagonists. Two MCR antagonists have been employed in such studies by various investigators, SHU-9119 [38] (Fig. **1C**) and HS-014 [39] (Fig. **1D**).

A large variety of other peptidic MCR agonists have been reported both in the scientific and patent literature; however, their efficacy in producing penile erection behavior remains largely unknown. One peptide derivative, HP-228 (Fig. **1E**) developed at Trega Biosciences [40], has been described in patent literature as

inducing penile activity in a rat model after IP administration at 1.8 mg/kg.

Among the small molecule agonists for MC-4R reported so far, THIQ (Fig. **1F**) [41-42] MB-243 (Fig. **1G**) [43], and RY-764 (Fig. **1H**) [44] developed at Merck & Company and an isoquinoline based compound developed at Trega Biosciences (TRG-2411#203; [45-46]; Fig. **1-I**) have been reported to induce penile erection. THIQ (MC-4R Ki 2nM) is an MC-4R selective agonist that has been studied in detail in rat models. This molecule models a constrained His-Phe-Arg-Trp tetrapeptide (or a tripeptide thereof) of α-MSH. All three small molecules, THIQ, MB-243, and RY-764, are orally bioavailable compounds. An oral dose of 10-40 mg of MB-243 caused 10-50% increase in penile erections in an *ex-copula* model in a dose dependent manner. Oral efficacy of RY-764 has not been reported. However, it has been reported to augment magnitude and duration of electrically stimulated erectile activity upon IV administration of 1 mg/kg dose in mice [44]. There was no effect on erectile activity at 0.1 mg/kg dose. In the absence of electrical stimulation it failed to show any stimulation of erectile activity. Not much is known about TRG-2411#203 and its pharmacological profile except that it was reported to induce penile erection at an IP dose of 3.6 mg/kg.

Among all the MC-4R agonist molecules, peptides and small molecules described for producing erectile response in animal models, only bremelanotide has been reported in the literature to have advanced to randomized human clinical studies. However, with the recent identification of several orally active MCR agonists, it is plausible that other clinical candidates for treatment of sexual dysfunction may emerge.

ANIMAL MODELS FOR THE *IN VIVO* STUDY OF MELANOCORTINS IN SEXUAL DYSFUNCTION

Male Sexual Dysfunction

Commonly, three different types of rat models have been utilized in studying penile erection by MCR agonists. A behavior model measuring spontaneous penile erection in normal rats has been used for most studies of bremelanotide [47]. This model allows measurement of the activity of an agent in initiating penile erection without any external (social) or experimentally induced sexual stimulus (drug or nerve stimulation). Using this model, 50 μg/kg of IN bremelanotide caused 100% of treated rats to have at least one erectile event and significantly increased the mean number of spontaneous erections during the 30-minute observation period following treatment [47]. ICV administration of bremelanotide is also erectogenic in male rats at much lower doses than that of IN administration [47]. Investigators at Merck [42] have used the *ex-copula* rat model for testing MCR agonists where reflexive erections are induced by the tactile stimulus of retracting the sheath surrounding the penis. An increase in frequency of penile erection by the agent is measured over the reflexive erections. A third model for the study of MCR agonists involves measurement of intera-covernosal pressure by telemetry in either anesthetized animals following electrical stimulation and drug treatment [44] or with a radiotelemetric pressure transducer implanted in the corpus cavernosum in a freely moving rat following drug treatment [48]. It is apparent, that due to complexity of this behavior/response, the translation of these data to humans remains to be validated. Nonetheless, it is prudent to note that these studies are often part of much larger research efforts, both at the academic institutions and pharmaceutical industry, to develop MCR agonists for the treatment of erectile dysfunction.

Female Sexual Dysfunction

The easily manipulated rat models for female sexual behavior are commonly used because female rats express sexual behavior only when circulating sex steroids are at particular levels during the rat estrus cycle. By removing the ovaries of the rat, injecting the appropriate hormones to prime the system for sexual receptivity and exposing the female to a male rat, sexual behavior can be observed. This also allows for the evaluation of pharmacologic intervention. Most pharmacological studies of female sexual behavior have focused on lordosis behavior. Lordosis is a posture assumed by a sexually receptive female rat in which she arches her back, thereby allowing intromission by the male. Many endogenous neurotrans-mitters and many pharmacological agents play a role in affecting lordosis, which is considered the consummatory component of female rat sexual behavior. However, before lordosis is expressed by a hormonally primed, sexually receptive female rat, there is a series of appetitive, pre-copulatory solicitation behaviors that she may express. These behaviors are used by the female rat to signal the male that she is interested. Solicitation behaviors are considered to be analogous to human sexual arousal or desire [49-52]. Subcutaneous injection of bremelanotide to hormonally primed female rats selectively increased solicitation behaviors towards male rats, without affecting expression of lordosis behavior [52]. Data from this animal model suggest that bremelanotide selectively and strongly activates central mechanisms involved in sexual arousal in females that may be analogous to central mechanisms of arousal, motivation and desire in human females [52].

MECHANISM OF ACTION AND SITES OF ACTION OF BREMELANOTIDE

MC agonists exert their effects on sexual function via action on receptors in the central nervous system. Studies using MT-II showed that this agent had no direct effect on strips of cavernosal tissue *in vitro* and had no direct effect on erectile function when injected into the corpus cavernosum, but increased erectile activity in rats if administered ICV or IV [53]. Bremelanotide increases the frequency of erections in male rats when dosed IV, ICV or IN. This can be blocked by ICV administration of the MCR antagonist SHU-9119. Furthermore, ICV injection of bremelanotide in rats initiated erectile activity at doses >100 fold lower than required if administered systemically [47].

Besides receptor mapping, receptor binding, receptor antagonist studies and behavioral studies, another powerful tool to examine site of action of drugs in the brain is to map the neurons or brain regions that are activated or stimulated after a particular drug exposure by labeling the immediate early gene products (e.g., Fos) that are expressed. This technique has been widely used in neuroendocrine systems to measure and map neuronal activity [54]. In male rats, the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus are stimulated and express the immediate early gene product Fos after exposure to an efficacious IN dose of bremelanotide [47]. These regions also express melanocortin receptor subtypes 3 and/or 4 [55-56] and are associated with expression of male sexual behavior [57]. In addition, electrical stimulation of the PVN increases intracavernous pressure and erections in male rats, and thus the PVN is considered a central regulator of penile erections [58]. Tract tracing studies have shown that the PVN projects through other brain regions to the corpora cavernosa of the penis [47, 59].

Taken together, these data have lead to the presumption that bremelanotide initiates penile erection by action on MCRs in the hypothalamus that stimulates the peripheral production of nitric oxide from nerve endings in the corpora cavernosa, which promotes penile erection (Fig. **2**). Stimulation of hypothalamic MCRs likely also impacts sexual function and erection via release of oxytocin [42, 60] as well as other neurotransmitters [48].

In females, the mechanism of action may be more complex. After subcutaneous injection of bremelanotide, female rat brains express Fos in the nucleus accumbens, medial preoptic area, ventral tegmental area, arcuate nucleus and the medial and basolateral amygdala [61]. These brain regions are involved in the regulation of

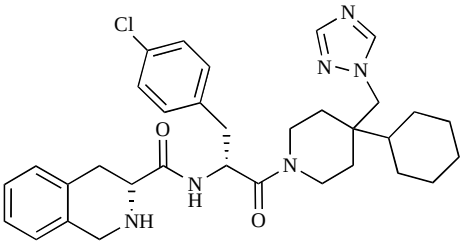
A Ac-Nle-Asp-His-D-Phe-Arg-Trp-Lys-NH_2 — MT-II

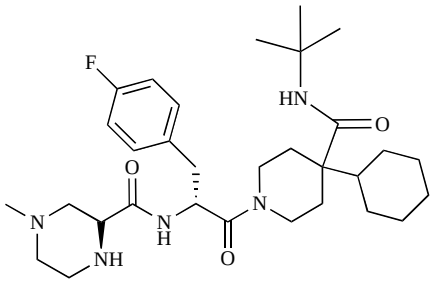
B Ac-Nle-Asp-His-D-Phe-Arg-Trp-Lys-OH — Bremelanotide (PT-141)

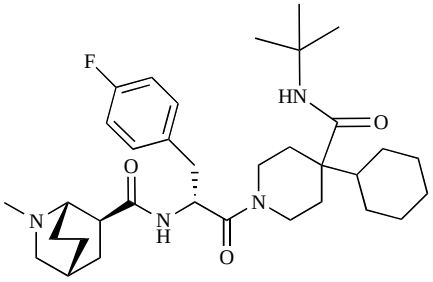
C Ac-Nle-Asp-His-D-Nal 2'-Arg-Trp-Lys-NH_2 — SHU-9119

D Ac-Cys-Glu-His-D-Nal 2'-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp-NH_2 — HS-014

E Ac-Nle-Gln-His-D-Phe-Arg-D-Trp-Gly-NH_2 — HP-228

F  — THIQ

G  — MB-243

H  — RY-764

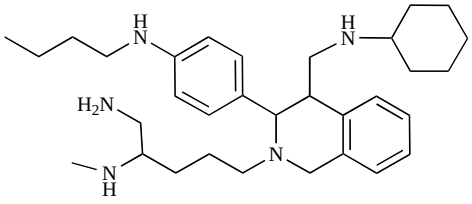
I  — TRG 2411#203

Fig. (1). Melanocortinergic agents that affect penile erection and have a role in the study or treatment of sexual dysfunction. **A:** MT-II, a synthetic analog of alpha-melanocyte stimulating hormone and MCR agonist **B**: Bremelanotide (PT-141), is similar to MT-II but it has a carboxylate group at its C-terminal instead of an amide. The structural difference between MT-II and bremelanotide has increased the therapeutic window for bremelanotide in the treatment of sexual dysfunction. **C:** and **D:** SHU-9119 and HS-014 are MCR antagonists used in studies to determine the MCR subtype specificity involved in sexual function. **E:** HP-228, a peptide derivative and MCR agonist that induces penile activity in rat model, after IP administration. **F-H:** THIQ, MB-243 and RY-764 are small molecule MCR agonists that are orally available and increase penile erections in rodent models. **I:** TRG-2411#203, is an isoquinoline compound with a largely undetermined pharmacologic profile has been shown to induce penile erections after IP administration.

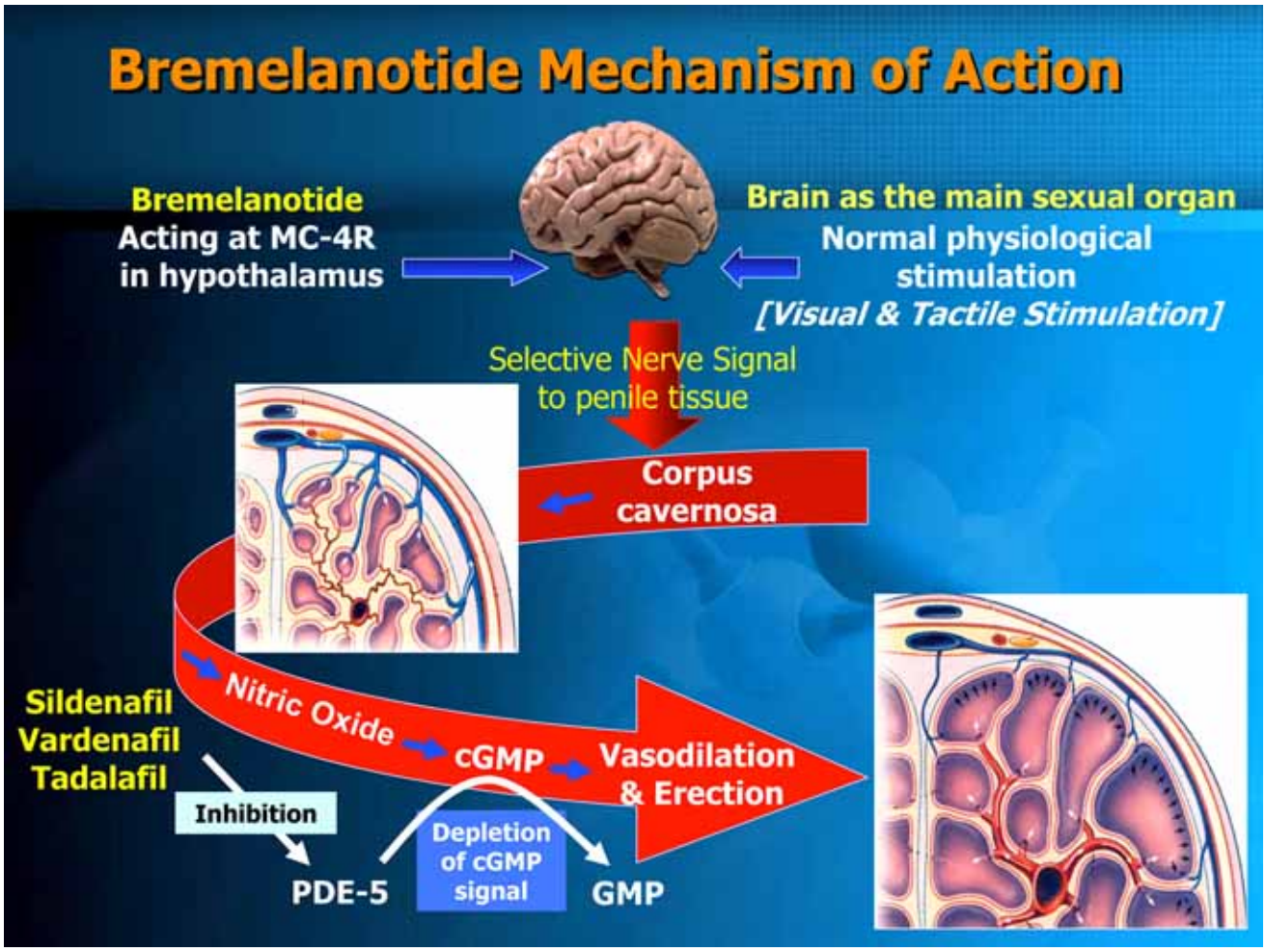


Fig. (2). Bremelanotide mechanism of action: Under normal physiological conditions, sensory systems send information about sexual stimulation to specific brain regions, which then send a selective nerve signal to the corpora cavernosa of the penis and stimulates nitric oxide (NO) release. NO binds soluble cytosolic guanylyl cyclases, thereby increasing cyclic GMP (cGMP) which in turn causes vasodilation and penile erection. However, this process also catalyzes phosphodiesterase-5 (PDE-5) phosphorylation. PDE-5 binds cGMP which is then hydrolyzed to 5'-GMP, which is not active. Orally administered sildenafil, vardenafil and tadalafil selectively inhibit PDE-5, thereby preventing the hydrolysis of cGMP. This increases or facilitates vasodilation and erection. In contrast, intranasally administered bremelanotide acts centrally on melanocortin 3 and 4 receptors to stimulate specific nuclei within the hypothalamus that project (via other brain regions) to the corpora cavernosa of the penis. This central melanocortinergic stimulation produces a local increase in NO within the penis, which initiates or causes vasodilation, engorgement and penile erection.

motivation, arousal and the appetitive components of sexual behavior [49]. The selective stimulation of these regions and mesolimbic dopamine pathways suggest that even peripheral administration of bremelanotide primes the brain regions involved in motivation and arousal in females [61].

INTRANASAL ADMINISTRATION OF BREMELANOTIDE

Because of the unique central mechanism of action for MCR agonists in treating sexual dysfunction, bioavailability and route of administration become important concerns, especially because the route of administration may impact patient acceptance, treatment adherence or treatment withdrawal. Recent studies suggest that there is a direct nose-to-brain pathway that allows direct central nervous system access to intranasally administered peptides. In one study of 36 healthy men and women, mean cerebral spinal fluid (CSF) concentrations of intranasally administered MSH/ACTH (4-10), vasopressin and insulin began to rise within 10 minutes of their respective administration. MSH/ACTH (4-10), concentrations in CSF peaked within 30 minutes, and all 3 peptides appeared to enter and concentrate in the CSF without a concurrent concentration increase in the blood-stream [62]. After a high dose (10 mg), MSH/ACTH (4-10) concentration in the CSF was still significantly higher than with placebo 100-120 minutes after administration [62]. The possibility of a direct pathway, allowing rapid access of peptides to the CSF, marks a new era for patients of easy self-administration of peptidic agents such as bremelanotide.

CLINICAL STUDIES ON MCR AGONISTS FOR TREATING SEXUAL DYSFUNCTION

The vast preclinical data demonstrating the effects of MCR agonists on erectile function has led to clinical trials to determine its utility in treating ED. In a recent double-blind, placebo-controlled study of bremelanotide use in healthy males as well as males diagnosed with mild to moderate ED, but who responded well to sildenafil, intranasal doses between 7 and 20 mg resulted in dose-dependent increases in erectile responses as measured by plethysmographic device called a RigiScan® [63]. This device continuously measures penile responses via displacement of sensor

loops at the tip and base of the penis [63]. The onset of the first erection after bremelanotide administration was typically 30 minutes and the doses were well tolerated. The mean serum half life was similar in all dose groups (range 1.85-2.09 h) and median T_{max} was 0.5 hours [63]. Flushing and nausea were the most common adverse events and were generally mild [63]. In another study of healthy males as well as males diagnosed with ED who had inadequate response to sildenafil, subcutaneous injection of either 4 or 6 mg of bremelanotide produced a statistically significant erectile response [64]. This study showed that bremelanotide is effective in initiating erections in men with treatment-refractory ED and severe ED [64]. Moreover, another pilot study showed that co-administration of low doses of PDE-5 inhibitor (sildenafil, 25 mg oral) and bremelanotide (7.5 mg intranasal) to males with ED resulted in significantly greater erectile response than sildenafil alone (in the context of sexual stimulation), suggesting a possible synergistic effect and opening up the possibility to treat patients with severe ED without exacerbating the side effects of either treatment [65].

The initiation of erections in healthy men who took bremelanotide without any visual sexual stimulation [63-64] distinguishes the mechanism of action of bremelanotide from other ED treatments that act to facilitate erections (e.g., PDE-5 inhibitors), but require sexual stimulation for pharmacologic activity. Treatment failure is not uncommon with PDE-5 inhibitors [18], and is often associated with neurogenic and vascular disorders, but treatment failure can also be related to decreased efficacy and lack of sexual stimulation [19]. Agents like bremelanotide that do not require additional sexual stimulation may present a therapeutic advantage by instilling confidence in the ED patient prior to initiating sexual activity. Due to their mechanism of prolonging the effects of NO release, PDE-5 inhibitors are contraindicated with vasodilators such as nitrates. Conversely, bremelanotide does not cause systemic vasodilation and therefore does not cause hypotension.

In women, a randomized, double-blind placebo-controlled, crossover pilot study was conducted to determine the effect of bremelanotide on sexual response in 18 premenopausal women diagnosed with FSAD [66]. After a single dose of intranasal bremelanotide, visual sexual stimulation (erotic videos) was not associated with increased vaginal vasocongestion as measured by vaginal photoplethysmography. However, qualitative measures of arousal and desire, which were measured by subjective interviews and questionnaires, revealed a trend towards increased genital arousal and a statistically significant increase in desire after bremelanotide administration [66]. These measures also showed that women who had intercourse within the 24 hour period following bremelanotide treatment were significantly more satisfied with their subjective level of arousal compared to those who were treated with placebo [66].

These clinical data from both men and women correlate with observations from animal studies of bremelanotide as a centrally acting agent affecting pathways involved in desire and arousal responses. Although the clinical research seems promising and validates the utility of this active MCR agonist in the treatment of ED and FSAD, the data are limited to phase II trials. Additional data from Phase III trials will provide definitive efficacy and tolerability information within the context of intimate sexual encounters in the home setting. The advantages of bremelanotide thus far include a low incidence of adverse events, a short half life, and the lack of contraindication of nitrate drugs that contributes to a good safety profile. In addition, bremelanotide has a relatively rapid onset of action and a unique mechanism of action compared to the standard of care. Overall, these results validate the MC system as a viable drug target for the treatment of male and female sexual dysfunction.

CONCLUSIONS

Clinical data have shown that bremelanotide is an erectogenic agent in both healthy males and males diagnosed with ED, and this MC agonist holds promise as a potential new approach to treating ED. Clinical data from proof of principle studies on women with FSAD suggest that bremelanotide can influence subjective arousal and desire. Preclinical data support the assertion that bremelanotide acts on MCRs in the hypothalamus to increase sexual arousal or desire. The availability of an effective agent that is easy to administer, with a rapid onset of action and acceptable tolerability, may allow men and women currently with no viable treatment alternatives to obtain treatment for their sexual dysfunction. Ongoing and future clinical studies examining efficacy of bremelanotide in both males and females in a more relevant sexual context of an at-home environment will more fully address its therapeutic relevance and benefit.

ABBREVIATIONS

Alpha-MSH	=	Alpha-melanocyte stimulating hormone
CNS	=	Central nervous system
ED	=	Erectile dysfunction
FSAD	=	Female sexual arousal disorder
ICV	=	Intracerebroventricular
IP	=	Intraperitoneal
IV	=	Intravenous
MC	=	Melanocortin
MCR	=	Melanocortin receptor
MT-II	=	Melanotan-II
NO	=	Nitric oxide
PDE-5	=	Phosphodiesterase-5
POMC	=	Pro-opiomelanocortin
PVN	=	Paraventricular nucleus
SAR	=	Structure/Activity relationship
SC	=	Subcutaneous
SON	=	Supraoptic nucleus

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