Endocrine
DOI 10.1007/s12020-014-0520-7

MINI REVIEW

Hormonal correlations of premature ejaculation

Andrea Sansone · Francesco Romanelli · Emmanuele A. Jannini · Andrea Lenzi

Received: 18 November 2014 / Accepted: 21 December 2014

Abstract Premature ejaculation is the most frequent male sexual dysfunction, significantly impairing quality of life of both the patient and the partner and affecting up to one-third of men of every age. In the last years, our knowledge about this topic has greatly increased, and studies on the causes and treatments related to ejaculatory disorders have shed a light on previously uncharted territory. Public interest on sexual dysfunctions has likewise increased in the general population: the time lapse between the first symptoms of sexual dysfunction and the seeking of medical advice has been significantly reduced, whereas demand for a treatment has markedly increased. A role of endocrine regulation has been established in all the aspects of male reproduction; however, the endocrine control of ejaculation is not fully understood. Sex steroid, pituitary, and thyroid hormones have all been advocated as potential candidates in the regulation of the ejaculatory process, but exact mechanisms are not clear yet and further studies are required in order to identify potential targets for treatment.

Keywords Premature ejaculation · Orgasm · Hormones · Delayed ejaculation

A. Sansone (✉) · F. Romanelli · A. Lenzi
Section of Medical Pathophysiology, Food Science and Endocrinology, Department of Experimental Medicine, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy
e-mail: andrea.sansone@uniroma1.it; andreasansone85@gmail.com

E. A. Jannini
Department of Systems Medicine, Tor Vergata University of Rome, Via Montpellier, 1, 00133 Rome, Italy

Introduction

Although consistent information about its prevalence is lacking [1], premature ejaculation (PE) is the most frequent male sexual disorder [2]: according to different criteria, its prevalence might widely vary, ranging from 8 to 30 % [3] up to 22–38 % [4] in all age groups, yet very few men seek treatment. PE is "a culture-dependent symptom that is self-identified, self-reported, and self-rated". For this reason, a conclusive definition is hard to reach: many authors and several scientific societies have provided different definitions of PE [5], classifying PE on time of onset, pathogenesis, and situational occurrence. Nonetheless, three common constructs underlie most definitions of PE: (1) brief ejaculatory latency; (2) loss of control; and (3) psychological distress in the patient and/or partner.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) definition of PE includes the approximately 1-minute intravaginal ejaculatory latency time (IELT) criteria as well as the inclusion of distress. It also asks the clinician to specify the subtypes of lifelong and acquired, generalized, or situational dysfunction as well as its severity. Anteportal ejaculation is the term applied to men who ejaculate prior to vaginal penetration and is considered the most severe form of PE [6].

In 1917, PE was considered a symptom of neurosis, requiring psychoanalysis; in later years a more "psychobiological" view was hypothesized and PE was considered a psychosomatic disorder [7]. In the seventies, Masters and Johnson postulated that PE occurred as the result of a learned behavior; this definition was considered the most up to date until the end of the century, when Waldinger identified genetic and neurobiological determinants of PE [8, 9]. A "Manichean" distinction between psychogenic and organic pathogenesis of PE is under close scrutiny, and

Published online: 01 January 2015

represents one of the most frequent controversies in sexual medicine [10, 11]: neurotransmitters are involved as much as psychological issues [12], partially explaining the differences between lifelong and acquired forms of PE.

However, it is important to consider the fundamental role of the partner in determining the development of PE. In fact, PE is maybe the only partner-oriented male sexual symptom, since the ejaculatory precocity refers to partner sexual physiology and to the time course of the female sexual response [13]. Hence, the PE lives only inside of the couple.

In the field of male sexual dysfunctions, PE and erectile dysfunction (ED) are frequently coexistent in the same subject [14, 15]: based on their role on erectile function and sexual drive, hormones have been recently investigated in order to assess the exact endocrine mechanisms pertaining to ejaculation.

Androgens play a pivotal role in preserving sexual health [16, 17], but many other hormones are somehow involved in erectile function [18, 19]: even if more recent papers have provided a better insight on the endocrine control of the ejaculatory reflex [20, 21], existing guidelines on premature ejaculation provide little information on this matter [22–25]. The aim of this review is to provide a quick, easy-to-read reference which might be useful to the physician during clinical practice.

Testosterone

The role of testosterone in maintaining male sexual health has been elucidated in many papers, though its association with PE is still unclear [26]. It has been proven that testosterone affects the ejaculatory process [27], improving the control of ejaculation. In humans, testosterone acts on a peripheral level by regulating the expression and activity of nitric oxide (NO) synthase and type 5 phosphodiesterase (PDE5); It is known that high levels of intrapenile nitric oxide act as a local neurotransmitter to facilitate the relaxation of intracavernosal trabeculae, thereby maximizing blood flow and penile engorgement. In addition, the NO-PDE5 system also affects the ejaculation process by regulating the contractility of the male genital tract [28, 29]. As a result, a low testosterone level may reduce the volume of ejaculate in hypogonadal patients [30] leading to a delayed ejaculation. Clinical studies have confirmed those pathophysiological aspects of testosterone showing that hypogonadal men are usually prone to develop delayed ejaculation, whereas higher levels of testosterone are often correlated to PE.

In animal models, testosterone has proven to be able to exert its effects on different levels: at hypothalamic level, higher levels of testosterone are able to suppress serotonin, leading to a development of PE [31], whereas at spinal level testosterone regulates nuclei involved in the control of ejaculation. These findings, however, have yet to be confirmed in humans.

In addition, the literature evidence regarding the gonadotropins role related to PE is still severely lacking. A recent research found no significant correlation between luteinizing hormone (LH) and PE, although patients with PE had significantly higher levels of follicle stimulating hormone (FSH) [32]; these results, however, disagree with previous findings on the same topic [26].

Estrogens

Antagonism between testosterone and estradiol is often suggested as a possible cause of ED [33–35]. Estrogens are classically involved in female sexual excitation, but their receptors (ER-α and ER-β) have been discovered in the epididymis of rabbits and other animal species [36]. Some authors have hypothesized that estrogens are also involved in epididymal contractility in humans and are designated to achieve fertility [37]. Furthermore, estrogens are fundamental for activities involving the sympathetic activity of smooth muscle cells [38], including sexual stimulation.

Oxytocin

Oxytocin is an oligopeptide synthesized in the paraventricular and supraoptic hypothalamic nuclei and secreted by the posterior pituitary gland and it is mostly known for its role in stimulating lactation; however, its role in males has not been fully investigated. Research on this topic has shown that oxytocin is a potent inducer of penile erection in rodents [39]; based on these findings, more recent studies have shown that oxytocin levels in human plasma greatly increase during orgasm [40]. In rats, oxytocin showed a facilitatory effect on ejaculation by reducing the ejaculatory latency time and post-coital refractory time [41]; on the other hand, rodents with lower oxytocin levels had longer mount and refractory time, providing further demonstration of a role of this hormone on ejaculation [42]. However, administration of exogenous oxytocin has not shown the expected results: in a small group of healthy men, intranasal application of oxytocin did not have any significant effect on sexual behavior [43]. On the other hand, oxytocin receptors blockade via highly selective antagonists has shown promising effects in treating PE [44]. Oxytocin facilitates male and female reproductive behavior [45]: increased central and peripheral oxytocin levels perhaps might provide an answer to the role of the serotoninergic system in facilitating erection, ejaculation, and penile detumescence [46]. There are still a few missing pieces from this puzzle but we can assume that research on

oxytocin and its relation to ejaculation disorders is far from being complete.

Prolactin

In female mammalians, prolactin (PRL) is involved in lactation; however, in males elevated PRL levels inhibit pulsatile secretion of gonadotropin-releasing hormone (GnRH), leading to a form of secondary hypogonadism. High PRL levels might impair sexual function in otherwise healthy men: this rarely happens in mild hyperprolactinemia (>20 ng/ml) but becomes a more common finding in severe hyperprolactinemia (>35 ng/ml). Elevated PRL is most commonly associated with delayed ejaculation, whereas lower PRL has been observed more consistently in patients suffering from PE; these findings have been confirmed even after adjusting for age, body mass index, medicaments, and smoking habit. Low PRL levels have also been observed in patients with high anxiety and guiltiness during masturbation, suggesting perturbations of the neurological pathway involving serotonin and its receptors. In a consecutive series of 2,531 outpatients consulting for sexual dysfunctions, PRL in the lowest quartile levels is associated with Metabolic Syndrome and ED, as well as with PE and anxiety symptoms [47]. However, in a recent study [32], no significant difference was found between PRL levels of subjects with PE and healthy men: it seems that there is still a lot to be discovered regarding the role of PRL in ejaculation disorders.

Thyroid hormones

The effect of thyroid hormones on human behavior has been thoroughly investigated. Receptors for thyroid hormones have been found in the male genital tract [48]: based on this assumption, a role of thyroid hormones in PE has been postulated [49]. Hyperthyroidism in animal models has been advocated as a possible cause, or even a risk factor, of premature ejaculation [50, 51]: even if the first studies in men did not lead to certain results [52], a role of thyroid hormones has been already confirmed in humans [53]. Treatment of hyperthyroidism has proven to be effective for PE: after normalizing thyroid function in hyperthyroid men, the prevalence of PE fell from 50 to 15 % [49]. A role for hyperthyroidism-induced anxiety in causing PE was also investigated [54, 55]. However, at multivariate analysis, even after adjusting for anxiety, a low TSH was independently predictive of PE [54]. It was also shown the medical treatment of the opposite state, hypothyroidism, resulted in a twofold decrease in ejaculatory latency [47]. Hence, both hyper- and hypothyroidism have been advocated as causes of sexual health disorders [56]: diagnosing and treating thyroid disorders might have lead to a significant improvement in quality of life. However, the assessment should be made only after performing careful medical history and physical examination, in order to evaluate the most common features and symptoms of hypo- or hyperthyroidism.

Adrenal hormones

To date, literature is severely lacking regarding the role of adrenal hormones in PE. Among adrenal androgens, androstenedione, DHEA, and DHEAS are undoubtedly the most important ones; however, only DHEA and DHEAS have been investigated as a possible cause of sexual dysfunction. The routine evaluation of DHEA and DHEAS has not been recommended in assessment of erectile function; as for what concerns PE, there are scanty evidences regarding the hormonal involvement in its pathogenesis.

Cortisol is undoubtedly the most known adrenal hormone: its role on metabolism has been thoroughly investigated, although evidence on its role on sexual dysfunction is still inconclusive. Stress management is involved in the pathogenesis of ED [57, 58]: considering the involvement of cortisol in coping with stress, we suppose that it might be interesting to evaluate cortisol levels in patients with PE, even if literature does not provide evidence in this regard.

Leptin

Leptin, a hormone identified in 1994 and traditionally associated with satiety and energy expenditure, has been extensively studied in the last decades in order to identify its roles on other physiological processes. Leptin is involved in the regulation of different elements of the hypothalamic–pituitary–gonadal axis [59, 60], and its production might also occur autonomously in human spermatozoa [61]: based on these assumptions, a role for leptin in premature ejaculation has been postulated and studied [62, 63]. Elevated serum leptin seems to be significantly associated with PE: however, these studies have been led on a small scale, and the authors themselves suggest that more studies are necessary in order to consider leptin a marker or a diagnostic tool for PE.

Conclusions

Premature ejaculation is the most common male sexual dysfunction, and yet its pathophysiology remains not

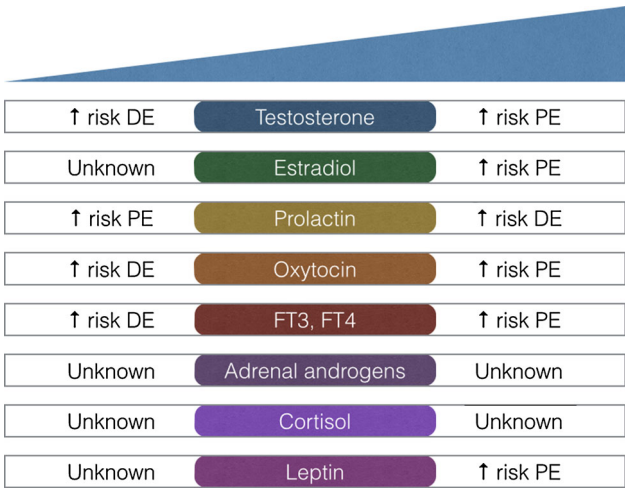

Fig. 1 Effects of different hormones on ejaculation. *PE* premature ejaculation. *DE* delayed ejaculation

completely understood [64], though chronic prostatitis [65–67], lack of privacy [68], and psychorelational/psychosexual issues [69] are considered important causes of PE. PE significantly affects the sexual life of the couple [13, 70], and has recently been identified as a frequent cause of relationship breakups [71]. Among the known secondary causes of PE, hormonal alterations might play a pivotal role; however, hormones are also frequently involved in other sexual disorders, therefore complicating the diagnosis (Fig. 1). Hyperthyroidism has been considered a cause of PE, and its treatment has been found effective in delaying ejaculation; low levels of PRL have been found in patients suffering from PE, although hypoprolactinemia might be a marker of perturbations in the serotonin pathway. There seems to be still little evidence in regards to the involvement of other hormones in the pathogenesis of PE. Hence, we suggest the evaluation of testosterone, estradiol, PRL, leptin, adrenal hormones, and thyroid functioning only when significant symptoms suggesting the suspect of underlying diseases are observed. It should be clear that PE is often associated with endocrine diseases, requiring adequate investigation and follow-up by a trained specialist: the endocrinologist should be a reference during differential diagnosis of PE.

Conflict of interest The authors declare no existing conflict of interest.

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