Recent Advances On The Male Contraceptive Pharmacology

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Las opciones anticonceptivas masculinas son mucho más limitadas que las femeninas, siendo los preservativos y la vasectomía las opciones en la mayoría de los países. Aún no se dispone de una píldora anticonceptiva masculina, aunque la investigación sobre el tema comenzó en el siglo pasado. No obstante, los ensayos clínicos recientes que prueban nuevas versiones de los fármacos anticonceptivos masculinos candidatos indican que habrá opciones más accesibles para los hombres en un futuro cercano. Analizamos estos supuestos fármacos en el presente artículo.

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RESUMEN

Actualmente se están desarrollando investigaciones que buscan nuevas opciones de tratamiento anticonceptivo masculino. Ya se ha recorrido un largo camino para encontrar candidatos farmacológicos adecuados para la anticoncepción masculina, pero parece que la ciencia está un poco más cerca ahora que antes. Los candidatos farmacológicos hormonales y no hormonales son el foco principal de la búsqueda de una píldora anticonceptiva masculina.

Palabras clave: fármaco anticonceptivo masculino, anticonceptivo hormonal, anticonceptivo no hormonal.

ABSTRACT

Research pursuing new male contraceptive treatment options are currently developing. A long way to reach suitable drug candidates for male contraceptive has already been made but it looks like science is a little bit closer now than before. Hormonal and non-hormonal drug candidates are the main focus on the search for a male birth control pill.

Key words: male contraceptive drug, hormonal contraceptive, non-hormonal contraceptive.

1.Introduction

Over the years, various female contraceptive options have been developed, such as oral, transdermal, vaginal and injectable, all by hormonal drugs, as well as intrauterine devices and surgical methods [4, 6]. These approaches, when administered correctly, guarantee the greatest effectiveness in controlling pregnancy among the existing methods [4, 5]. However, in the case of male contraceptives, there has been a stagnation in the development and research of reversible methods, especially after the popularization of condoms.

Currently, contraceptive options for men are scarce, such as vasectomy, which is invasive and hardly reversible, and condoms, which play an essential role in protecting against Sexually Transmitted Infections (STIs), but they have high failure rates, generally related to incorrect use and misinformation but also for manufacturer matters [6]. Even so, there has been a reduction in family size for years, evidenced by the fall in birth rates, which seems to be linked to socio-economic factors all over the world [1, 2]. This change however is partly due to the development of varied and more efficient female contraceptive methods, as well as their increased accessibility [1, 2]. Nevertheless, between the 2015 and 2019 years, data suggest that 48% of pregnancies were unplanned, which represents an annual worldwide rate of 64 unplanned pregnancies for every thousand women between the ages of 15 and 49. Moreover, most of the cases are concentrated in countries with a medium or low development index, highlighting the social, economic and demographic issues linked to unplanned childbirth [3].

On the other hand in recent years there has been growing interest in developing new, reliable and safe birth control options for men beyond condoms or vasectomy [6]. These include hormonal methods which despite facing multiple barriers, for instance systemic side effects, dosage regimens, routes of administration and the public stigma surrounding steroid use, are being developed in different pharmaceutical forms, such as oral pills, injectables and transdermal gels [7]. Male hormonal contraceptives target the hypothalamic-pituitary-gonadal (HHG) axis, leading to suppression of testicular synthesis of testosterone and sperm. In addition, there are also non-hormonal contraceptives which act on the various stages of spermatogenesis, limiting side effects and simplifying their use [7, 8].

2. Male hormonal contraceptives

The HHG axis functions as a classic negative feedback hormonal circuit, in which gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary gland [7], as depicted in Figure 1. These hormones stimulate the Sertoli and Leydig cells in the testicles respectively, inducing both testosterone (T) synthesis and sperm maturation. Serum testosterone binds to androgen receptors (ARs) throughout the body to exert physiological effects [6, 7]; for example, by binding to ARs in the hypothalamus and pituitary gland, they inhibit the release of GnRH and gonadotropins, thus connecting the feedback loop. Thereby, keeping that in mind, exogenous androgens might act as contraceptives by interrupting/inhibiting this circuit in a similar way to endogenous testosterone [7]. The hormones bind to peripheral ARs maintaining androgenic action in various tissues, such as muscles and skin, and also for libido. In addition, exogenous androgens suppress the production of GnRH, FSH and LH, as well as intratesticular testosterone synthesis and, consequently, spermatogenesis. Hence in the absence of high testosterone concentrations spermatogenesis is inhibited [7].

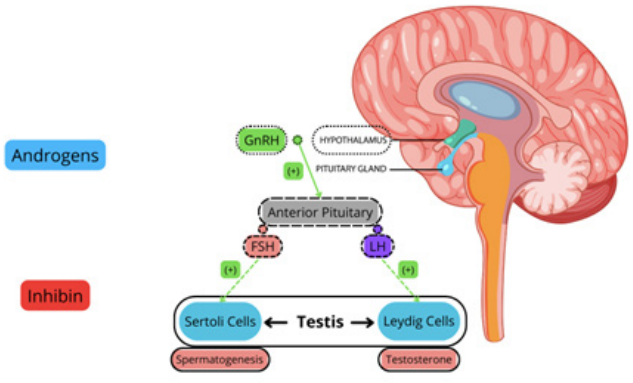

Figure 1: *The HHG axis. Hypothalamic-pituitary–gonadal axis physiology, the feedback mechanisms and contraceptive agents effect. The male hormonal contraceptive regimen leads to the inhibition of the production of endogenous testosterone and sperm*

"Currently, there are only two contraception options for men: vasectomy and the use of condoms"

The administration of exogenous testosterone as a contraceptive agent has been extensively studied, and we will discuss some results from pioneering and more recent clinical studies. Contraceptive efficacy studies are defined as studies in which the couple uses the agent under evaluation as the sole method of contraception, and it is necessary to demonstrate adequate sperm suppression to initiate them, and the participating men must reach a predetermined sperm concentration before entering the efficacy phase [7]. One of the first efficacy studies was conducted by the World Health Organization in seven countries, seeking to evaluate the hormonal induction of azoospermia in 271 healthy fertile men. The study used the drug testosterone enanthate (TE) at a dose of 200 mg administered intramuscularly weekly, and it was divided into two stages. In the first stage, approximately 70% of men presented azoospermia and only one case of pregnancy was recorded during the efficacy phase. In the second phase, it was revealed that with sperm suppression or severe oligozoospermia (<3 million/mL), contraceptive efficacy was high, with a failure rate of 1.4% and approximately 98% of men managed to achieve this target. However, it is worth to notice that androgenic adverse effects, such as mood changes, changes in libido, acne, weight gain and hypertension, besides to the need of consecutive injection applications, were the most common reasons for discontinuation and resistance of participants [9].

Furthermore, a pilot study on the daily application of 50-125 mg transdermal testosterone gel in association with oral 20 mg/day medroxyprogesterone acetate demonstrated contraceptive efficacy [10]. During the study, it was reported that serum testosterone concentrations remained stable at physiological levels, so there were no significant androgenic adverse effects and, simultaneously, the use of progestins facilitated the achievement of the desired contraceptive effect [10]. The results obtained throughout other studies in the same period suggested the existence of racial heterogeneity in the capacity of sperm suppression in response to hormonal methods, which was investigated by the WHO and other partners in a phase 2 study conducted on 4 continents between 2008 - 2012 with 320 participants [7, 11]. Despite the outstanding results, with 4 cases of pregnancy occurring among the partners of 266 men during the efficacy phase that lasted 56 weeks, the study was interrupted early on the recommendation of an external committee, mainly due to cases of moderate to severe depression in some patients at one of the sites studied. In addition, approximately 20 men discontinued the study due to adverse effects related to the drug, such as mood oscillation, pain and panic at the first application, palpitation, hypertension and erectile dysfunction [11].

" An effective, long-lasting but reversible contraceptive drug is strongly needed for men"

Efficacy studies have demonstrated over the years that the combined use of androgens with progestins in male contraceptive regimens can be effective and reversible, mainly because they minimize androgen doses and consequently reduce their adverse effects [7]. Based on this, new hormonal agents have been developed, targeting at the easiness of use and also the acceptability by users, such as the combined nestorone-testosterone gel (NES-T) and the oral prodrug 11β-methyl-19-nortestosterone-17β-dodecyl carbonate (11β-MNTDC) [6]. In 2019, Bradley D. Anawalt and his collaborators published a clinical study carried out within 44 healthy men who administrated 8.3 mg NES-T topic gel daily and 62.5 mg testosterone, which have proved to be effective and safe in suppressing gonadotropins, achieving 80% user fulfillment [12]. As a matter of fact, Nestorone is the brand name for segesterone acetate, which is a progestin derivative with negligible androgenic, estrogenic and minimal glucocorticoid activities at therapeutic doses, and few adverse effects [12]. According to the government source Clinical Trials, the study about NES-T gel is currently in phase II-b.

Back in 2019, Sherry Wu and her collaborators published a clinical study to analyze 11β-MNTDC, which is a precursor of 11β-methyl-19-nortestosterone (11β-MNT)

and has androgenic and progestational activity [13]. This clinical study has enrolled 12 healthy men who used escalating oral doses of 100, 200, 400 and 800 mg and aimed to evaluate the safety, tolerability and suppression of gonadotropins and testosterone by 11β-MNTDC [13]. The active agent, 11β-MNT, was able to bind to and activate human androgen and progesterone receptors; however, the prodrug had minimal activity at these receptors. From the results, it was possible to observe that single oral doses were well tolerated, with no significant adverse events, and administration with food consumption increased the serum concentration of both the precursor and the active substance. Finally, 11β-MNTDC at 200-800 mg range dose was able to markedly suppress serum testosterone concentrations, presenting themselves as a promising candidate for male hormonal contraception [13].

"The developing of a non-hormonal male contraceptive might avoid side effects related to hormonal drugs"

3. Male non-hormonal contraceptives

On the other hand, non-hormonal male contraceptives target one of the following pathways: [1] interrupting the maturation of sperm in the testicles; [2] blocking the effective transport of sperm by altering their motility or obstructing their path to the egg; or [3] inhibiting sperm-egg fusion. All the approaches offer the possibility of leaving the hormonal axis completely untouched, reducing the most harmful adverse effects on quality of life [6]. Common targets for that include, for example, testicular retinoic acid receptors and ion channels in sperm [6].

Retinoic acid plays an essential role in the maintenance of spermatogenesis and the male reproductive system, since Sertoli cells are totally dependent on vitamin A, which is largely stored in these cells [14]. A deficiency of the vitamin or the absence of retinoic acid receptors causes dysfunction in sperm synthesis and even sterility in males [15]. Thus, taking this information into account, one can discuss the development of new non-hormonal agents, such as YCT529 (Figure 2), an α-selective antagonist of the retinoic acid receptor (RAR-α). This protein is part of the family of trinuclear receptors that bind to retinoic acid, a form of vitamin A that plays an important role in cell growth, differentiation, including sperm formation, and embryonic development. Among approximately 100 synthesized compounds, YCT529 showed the greatest binding potency and selectivity to RAR-α and was tested orally in mice. After 4 weeks, there was a drastic reduction in sperm count and it was 99% effective in preventing pregnancy without noticeable adverse effects and it was reversibly after 4 to 6 weeks of discontinuing administration, presenting itself as a worthy candidate for *in vivo* studies [16]. Studies with YCT529 continued and a phase 1b/2a clinical study is scheduled to begin in August 2024, with the aim of evaluating efficacy, tolerability, pharmacokinetics, pharmacodynamics, and assessing sexual and emotional function [17]. The study will include healthy men who have decided to have a vasectomy and are awaiting the procedure and men who have decided not to have children in the future [17].

" A protein called the retinoic acid receptor alpha (RAR-α) is a target for a non-hormonal male contraceptive drug"

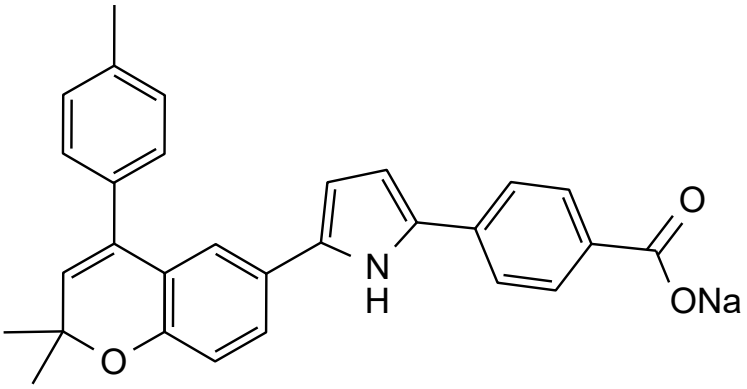

Figure 2: *YCT529 chemical structure.*

At the end of the last century, studies reported that calcium-dependent signaling regulates flagellar hyperactivity, responsiveness, and acrosomal motility of sperm [6, 18]. Among the various sperm-specific ion channels, there is CatSper channel, which is expressed only in mature sperm [18]. Four CatSper channels have been identified that play critical role in male fertility, according to knock-out mouse models [6]. In order to reach its full activity CatSper channels require some prior conditions such as intracellular alkalinization, presence of progesterone, and depolarization [18]. Other sperm-specific ion channels, such as KSpers K+ channels, such as Slo1 and Slo3, play an important role in the activation of CatSper channels and are potential pharmacological targets [19, 20]. RU1968 is a synthetic inhibitor of CatSper and SLO3 and recent results have demonstrated that it has high affinity for CatSper. However the mechanism of action has not yet been elucidated [21, 22, 23].

4. Conclusion

A long way to reach suitable drug candidates for male contraceptive has already been made but it looks like science is a little bit closer now than before. Surely the health systems all over the world would benefit of such drugs in special because data highlighted by Bearak *et al.*, quoted at reference number 3 at the list below, are really worrying. Well, working in progress.

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