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New approaches to male non-hormonal contraception

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Abstract

A non-hormonal male contraceptive is a contraceptive that does not involve the administration of hormones or hormone blockers. This review will focus on the use of lonidamine derivatives and inhibitors of retinoic acid biosynthesis and function as approaches to male non-hormonal contraception. Two current lonidamine derivatives, Adjudin and H2-gamendazole, are in development as male contraceptives. These potent anti-spermatogenic compounds impair the integrity of the apical ectoplasmic specialization, resulting in premature spermiation and infertility. Another approach to male contraceptive development is the inhibition of retinoic acid in the testes, as retinoic acid signaling is necessary for spermatogenesis. The administration of the retinoic acid receptor antagonist BMS-189453 reversibly inhibits spermatogenesis in mice. Similarly, oral dosing of WIN 18,446, which inhibits testicular retinoic acid biosynthesis, effectively contracepts rabbits. Hopefully, one of these approaches to non-hormonal male contraception will prove to be safe and effective in future clinical trials.

Keywords

lonidamine; adjudin; gamendazole; retinoic acid; contraception; spermatogenesis

1. Introduction

The world's population exceeds seven billion, is increasing by 80 million yearly and will likely reach 9–10 billion by 2050 [1]. Population growth is a leading cause of environmental degradation and human suffering from poverty and hunger [2]. Much of this population growth is unintended. In 2008, 41% of all pregnancies worldwide were unplanned, and 20% of all pregnancies ended in abortion, leading to 47,000 maternal deaths from unsafe abortions [3,4]. In the United States, the unintended pregnancy rate is 48%, and 18% of all pregnancies end in abortion, accounting for 1.1 million abortions annually [3]. This high rate of unintended pregnancy is due to inadequate use of and/or access to methods of contraception. Access to contraception dramatically reduces population growth and abortion rates, resulting in positive improvements in newborn and maternal health [5]. In addition to the attenuation in world population growth, the use of modern contraception and better maternity care worldwide has the potential to avert 1.7 million newborn deaths and 251,000

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maternal deaths each year [5]. Therefore, there is a great need for better access to existing contraceptives, better contraceptive education, and more contraceptive options both in the United States and around the world.

In the United States, 30% of all currently practiced contraception is male-directed with 20% of all couples using condoms and 10% of couples relying on vasectomy [6]. Both of these methods have significant drawbacks. Condoms, while providing some protection against sexually transmitted infections, have a marginal contraceptive efficacy [7], and vasectomy, which is expensive and difficult to effectively reverse, is most appropriately considered an irreversible method of male contraception [8]. A male contraceptive analogous to the estrogen/progesterone pills used by women would be welcomed by a large majority of men [9,10]. Importantly, 98% of women would trust their partner to use a male contraceptive [11]. Unfortunately, despite decades of research into hormonal and immunological methods of male contraception, no regimen based on either of these approaches is near clinical approval. There are numerous approaches to “non-hormonal” male contraception, which can be defined as male contraception that does not involve the administration of hormones or compounds that block hormone secretion or hormone action. Non-hormonal contraception may be more appealing to men as it avoids negative connotations associated with the use of anabolic steroids, and it may be more easily dosed orally than steroid preparations that are usually given by injection. In this review, we describe two promising approaches to male non-hormonal contraception. Firstly, we review the research on gamendazole and adjudin, two derivative of the potent anti-spermatogenic compound lonidamine, before discussing blockers of retinoic acid function and synthesis.

2. Adjudin

Adjudin is a lonidamine derivative that functions as a contraceptive by disrupting the adhesion of spermatids to the Sertoli cells, causing premature spermiation and infertility [12–14]. Administration of two doses of 50 mg/kg of adjudin (one dose per week) induced 100% infertility 5 weeks after treatment in adult rats. Fertility rebounded by week 11 [12]. The serum testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels did not change. Because there was some liver inflammation observed in a 29-day study of adjudin administration, researchers conjugated adjudin to a FSH β mutant specifically targeting it to Sertoli cells, thereby significantly reducing the dose necessary for contraception [15]. Unfortunately, the cost of this approach and the possibility of developing anti-FSH autoantibodies is a concern that needs to be addressed as the compound progresses to human studies [14].

3. H2-Gamendazole

H2-gamendazole is another lonidamine derivative that works by impairing the function of the apical ectoplasmic specialization [16]. In a recent study, fertile male rats received a single oral dose of gamendazole at 6 mg/kg [17]. This dose produced 100% infertility after a single oral administration; however, the drug only had 57% reversibility at this dose. Importantly, there was no significant difference in the circulating LH and testosterone levels with this dose compared to the control group, but FSH did increase, probably due to a reduction in inhibin B release from Sertoli cells. It should be noted that the mating behavior of the treated rats returned to normal and the first generation of offsprings of the animals who regained fertility did not appear to be affected. In terms of toxicology, three out of five rats died after receiving adose of 200 mg/kg of H2-gamendazole; however, no observable abnormalities including liver inflammation, necrosis or hemorrhage was detected at dosages lower than 200 mg/kg. As a result, researchers are preparing an investigational new drug

(IND) application to proceed to human testing, probably at doses of 1 mg/kg daily (personal communication)

4. Retinoic acid inhibition

It has been known since 1925 that vitamin-A (retinol) is required for normal spermatogenesis [18]. Nutritional studies in rats and genetic studies in mice demonstrate a requirement for vitamin-A and its metabolites at puberty for initiation of spermatogenesis and in adults for maintenance of spermatogenesis [19,20]. In the seminiferous tubules, both germ and Sertoli cells synthesize retinoic acid from retinal via aldehyde dehydrogenases [19]. Retinoic acid binds one of several retinoic acid receptors (RARs), which regulate gene expression. Male RAR knockout animals are sterile due to various problems in spermatogenesis [21–24]. Clearly, blockade of retinoic acid function or synthesis has the potential to inhibit spermatogenesis and is an appealing approach to male non-hormonal contraceptive development.

5. BMS-189453

BMS-189453 is an orally active retinoic acid receptor antagonist. At daily oral doses of 15, 60, or 240 mg/kg for 1 month, BMS-189453 produced marked testicular degeneration in rats, but also led to increases in leukocyte counts, alkaline phosphatase and alanine aminotransferase levels [25]. Significant overt signs of toxicity and deaths occurred at 240 mg/kg, whereas bodyweight and food-consumption decreases occurred at 60 and 240 mg/kg. When BMS-189453 was administered to male rats at daily doses ranging from 12.5 to 100 mg/kg for 1 week, only minimal testicular changes occurred at all doses [25]. This study, however, did not explore the fertility status of the animals nor did it look at reversibility of testicular changes after the study period. A recent well done study in mice explored whether a lower dose of BMS-189453 might function as a contraceptive without the toxicity seen at higher doses [26]. Two groups of 30 mice each were given BMS-189453 in oral dose of 5 mg/kg for 2 weeks (group 1) and 2.5 mg/kg for 4 weeks (group 2). The study showed that the mice were completely sterile by 4 weeks after a dosing regimen of 5 mg/kg and by the end of treatment with a dose of 2.5 mg/kg for 4 weeks. Infertility persisted for 2 weeks at the higher dose after cessation of treatment and was completely restored by 20 weeks in all but 1 male. In group 2, all males became infertile by the end of the treatment and infertility lasted for 4 weeks after cessation of treatment. By 12 weeks after treatment, fertility was completely restored in all males. The comparison of spermatogenic cell distribution in seminiferous tubules between the study and the control group at the end of the study showed that most of the tubules recovered completely. Hematology and serum chemistry analysis were unaffected by BMS-189453 administration. This compound, or a more specific retinoic acid- α antagonists [27–28] hold promise for non-hormonal contraception.

6. WIN 18,446

Almost 50 years ago, the oral administration of the bisdichloroacetyldiamine WIN 18,446 was shown to safely, completely and reversibly inhibit spermatogenesis in many species including man [29–32]. Histologic examination of testicular biopsies from men in these studies revealed a complete arrest of spermatogenesis, with an absence of forms beyond spermatogonia [32]. Since these compounds had no effect on the endocrine function of the testes, and were not androgenic themselves, it was concluded that the inhibition of spermatogenesis exhibited by WIN 18,446 was not hormonal in nature. At least 60 men received WIN 18,446 for up to one year with achievement of sperm concentrations below 1 million sperm/mL of ejaculate [29]—a sperm concentration associated with excellent contraceptive efficacy in trials of male hormonal contraceptives [33]. Unfortunately, subjects taking WIN 18,446 experienced a “disulfiram reaction” consisting of nausea,

vomiting, palpitations and sweating, when they drank alcohol [30]. Because of this, further development of WIN 18,446 was abandoned without an understanding of the mechanism by which it inhibited spermatogenesis.

Our group has recently demonstrated that WIN 18,446 suppresses spermatogenesis by inhibiting testicular retinoic acid biosynthesis [34]. In vitro, WIN 18,446 inhibits the function of aldehyde dehydrogenase 1A2, which functions in testicular retinoic acid biosynthesis. Using a rabbit model, we observed that oral administration of WIN 18,446 induced reversible azoospermia (Fig 1-upper panel). This reduction in spermatogenesis was preceded by a reduction in intratesticular retinoic acid (Fig 1 lower panel). These findings demonstrate that WIN 18,446 functions as an oral, non-hormonal male contraceptive by inhibiting the testicular biosynthesis of retinoic acid and suggests that inhibition of the testicular retinoic acid biosynthesis is a promising target for male contraceptive development. The development of novel, specific compound that inhibits testicular retinoic acid biosynthesis without interfering with alcohol metabolism is underway, and will hopefully result in compounds that reversibly inhibit spermatogenesis without significant side effects.

7. Discussion

Contraception is the most important tool to prevent unintended population growth and abortion, and increased use of contraception could decrease infant and maternal mortality and stabilize world population. New contraceptive technologies, especially effective male contraceptives, are likely to be widely used and accepted and would dramatically change the way in which contraception is provided around the world. Given the results in animal models, retinoic acid antagonists and/or lonidamine derivatives appear promising, and are leading to studies of these compounds in man aimed at determining their efficacy for the prevention of unintended pregnancy.

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Figure 1.

(Upper Panel) Sperm concentrations in New Zealand white rabbits treated with 200 mg/kg WIN 18,446 orally for 16 weeks (N=4). All animals were azoospermic between week 16 of treatment and week 8 of recovery. Animals underwent a hemi-orchietomy at the end of treatment, which accounts for the 50% reduction in sperm output at the end of recovery. *p<0.05 compared with baseline.

(Lower Panel) Testicular tissue retinoic acid concentration (pmol/g of tissue) in New Zealand white rabbits treated with 200 mg/kg WIN 18,446 daily, orally over time (N=4/group). Note the reduction in intra-testicular retinoic acid before the reduction in ejaculated sperm concentrations was observed. There were no significant changes in serum testosterone concentrations (not shown). All values are means $\pm$ SEM. * $p < 0.05$ compared with placebo, ** $p < 0.01$.

Figures are from Amory et al. *J Andrology* 2011; 32(1):111-119 (ref. 34)